

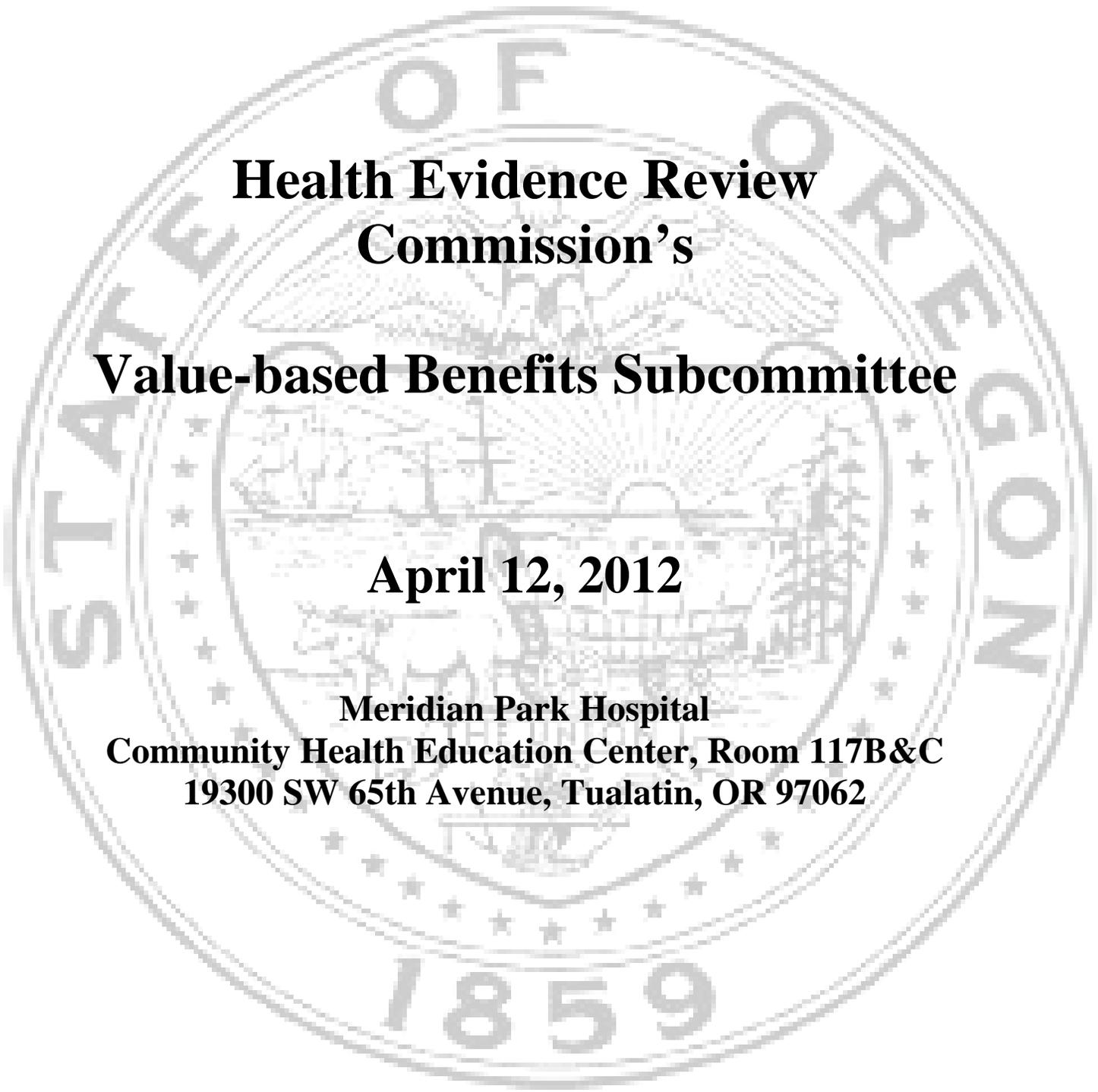


**Health Evidence Review  
Commission's**

**Value-based Benefits Subcommittee**

**April 12, 2012**

**Meridian Park Hospital  
Community Health Education Center, Room 117B&C  
19300 SW 65th Avenue, Tualatin, OR 97062**



**AGENDA**  
**VALUE-BASED BENEFITS SUBCOMMITTEE**  
**April 12, 2012**  
**8:30am - 1:30pm**  
Meridian Park Hospital  
Community Health Education Center, Room 117B&C  
19300 SW 65th Avenue, Tualatin, OR 97062  
*A working lunch will be served at approximately 12:00 PM*  
*All times are approximate*

- I. Call to Order, Roll Call, Approval of Minutes – Lisa Dodson 8:30 AM**
- II. Staff report –Ariel Smits, Cat Livingston, Darren Coffman 8:40 AM**
- III. ICD 10 – Cat Livingston and Ariel Smits 8:45 AM**
  - A. Podiatry—with Dr. Clifford Mah
  - B. Dermatology—with guests
  - C. Sports medicine
  - D. Oral maxillofacial surgery
  - E. Burns
  - F. Plastic Surgery
  - G. Neurology
- IV. New Discussion Items - Ariel Smits 11:00 AM**
  - A. Pulmonary valve repair
  - B. Nasal endoscopy for acute sinusitis
- V. Previous HOSC/HSC Discussion Items – Ariel Smits 11:30 AM**
  - a. Vascular bone grafts for avascular necrosis of the hip—with Dr. Adam Mirarchi by phone
  - b. Paraphilia line placement
  - c. Neoplasm of uncertain behavior
  - d. Cardiac MRI for thoracic aneurysms
- VI. Guidelines 12:15 PM**
  - a. Earlier implementation of guideline changes from ICD-10 review process
    - i. Urology guideline follow-up from ICD-10 review
    - ii. VAD guideline clarification from ICD-10 cardiothoracic surgery review
  - b. ESA guideline modifications
- VII. Straightforward - Ariel Smits 12:45 PM**
  - A. Straightforward table—April, 2012
  - B. Partial and total colectomy CPT codes
- VII. ICD 10 additional topic – Cat Livingston 1:00 PM**
  - A. Otolaryngology – with Dr. Paul Flint
- IX. Public Comment 1:25 PM**
- X. Adjournment – Lisa Dodson 1:30 PM**

# **Section 1**

## **Minutes**

## **Value-based Benefits Subcommittee Recommendations Summary**

*For Presentation to:*

Health Evidence Review Commission on April 12, 2012

*For specific coding recommendations and guideline wording, please see the text of the 3/8/12 VbBS minutes.*

### **CODE MOVEMENT**

- Coverage for continuous glucose monitoring for diabetes was removed from the Prioritized List
- Coverage was added for HPV vaccination for males. The age for coverage of HPV vaccination for males and females was changed to ages 9-26
- The diagnosis of lichen sclerosus on a covered line
- Tympanostomy tubes were removed from Line 383 Hearing loss, and the intent was clarified

### **ITEMS CONSIDERED BUT NO CHANGES MADE**

- Coverage of vascularized bone grafting as a treatment for avascular necrosis of the hip was not discussed. This topic will be addressed at the April meeting

### **GUIDELINE CHANGES**

- None

### **CHANGES FOR THE OCTOBER 1, 2013 PRIORITIZED LIST AS PART OF THE ICD-10 CONVERSION PROCESS**

- Specialty group recommendations review: Family Medicine, Nephrology, Vascular surgery, Gastroenterology, Urology, Allergy, Heart Transplant, Pediatric Surgery
- Multiple lines were renamed
- Multiple lines were deleted or merged
- New guidelines were created and two existing guidelines were modified as shown in Attachment A
- Line 570: SUBLINGUAL, SCROTAL, AND PELVIC VARICES was rescored to approximately line 550
- New line was created for FOREIGN BODY IN GASTROINTESTINAL TRACT and scored to the low 400s
- New line created for OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM and scored to approximately line 40
- New line was created for ANGIOEDEMA and scored to approximately line 520
- New line was created for HEREDITARY ANGIOEDEMA and was scored to approximately line 166
- New line was created for ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS and was scored to approximately line 390

### **CHANGES FOR THE OCTOBER 1, 2013 PRIORITIZED LIST AS PART OF THE BIENNIAL REVIEW**

- Line 513 GENDER IDENTIFICATION DISORDER, PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS was divided into two separate lines, Line XXX GENDER IDENTIFICATION DISORDER DYSPHORIA (scored to approximately line 430) and Line XXX PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS (scoring was not completed)

- Histrelin (Supprelin) insertion (GnRH analog used to suppress puberty) CPT (11981-11983) codes were added to new gender dysphoria line
- A new guideline was adopted for the new Gender Dysphoria line to specify included treatments
- The esophagitis line was reranked to approximately Line 540

DRAFT

## MEETING MINUTES

### VALUE-BASED BENEFITS SUBCOMMITTEE

#### Meridian Park Health Education Center

**March 8, 2012**

9:00 AM – 1:00 PM

**Members Present:** Lisa Dodson, MD, chair; Kevin Olson, MD, vice-chair; James Tyack, DMD; Chris Kirk, MD; Laura Ocker LAc.

**Members Absent:** Mark Gibson; Irene Crowell RPh.

**Staff Present:** Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Dave Lenar.

**Also Attending:** Isabel Bickle; and Denise Taray, DMAP; Jessie Little, ASU; Camille Kerr & Chris Doyle, Allergan; Heidi Allen, LCSW, Providence Health Systems; Jenn Burleton, Trans Active Education & Advocacy; Aubrey Harrison, Basic Rights Oregon.

The meeting was called to order at 9:05 AM. Roll call was done. Laura Ocker, LAc was introduced as a new member. Minutes from the February, 2012 VbBS meeting were reviewed and approved. ACTION: HERC staff will post the approved minutes on the website as soon as possible.

Smits gave the staff report. ICD-10 implementation has been delayed by the Centers for Medicare/Medicaid Services (CMS). The new implementation date has not yet been announced. HERC staff will move forward with the ICD-10 conversion process for the Prioritized List, as this process is about 80% completed. If ICD-10 is significantly delayed (2 or more years), then HERC staff will indentify important changes suggested to the List through this process and work to implement them in ICD-9 in a new version of the List.

*Note: All ICD-10 review changes take effect with the next Biennial Review Prioritized List (October 2013 or later)*

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#### Topic: **Straightforward Items**

**Discussion:** Smits reviewed the new process for approving the straightforward items. Committee members will review the items prior to the meeting and bring any concerns or desired changes to the meeting. The three items on the March agenda under straightforward had no concerns or desired changes and were approved as presented in the meeting packet.

**Actions:**

- 1) Add 33406 to line 237
- 2) Add 22305 and 22310 to line 507
- 3) Add 63045-63048 to line 271
- 4) Add 27075-27078 to line 208.
- 5) Add 11620-11626 to lines 275 and 311
- 6) Delete 38542 from Diagnostic Procedure File. Add 38542 to line 221
- 7) Add 66020 to line 413

- 8) Remove 403.91 from line 366. Add 403.91 to line 66. Keep 403.91 on 110
- 9) Add 382.9 to line 502
- 10) Add 27884 and 27886 to line 448
- 11) Add 27886 to line 308
- 12) Remove 17340 from lines 292, 524, 534, 618, 642, and 652
- 13) Remove 273.4 from line 479. Add 273.4 to lines 254 and 255
- 14) Add 77301 to line 197
- 15) Add 626.9 to line 446
- 16) Add 60521 and 60522 to lines 276 and 402
- 17) Delete 20605 from line 378
- 18) Add 29305 and 29325 to line 336
- 19) Add 31603 to line 14
- 20) Add 44125 to line 84
- 21) Add 43249 to lines 71 and 126
- 22) Add 50546 to line 54
- 23) Add 50650 to line 96
- 24) Add 29150 to line 250
- 25) Add 77301 and 77470 to line 275
- 26) Remove 44799 from line 111. Advise DMAP to add 44799 to Ancillary List
- 27) Add 37609 to line 117. Advise DMAP to remove 37609 from the Diagnostic Procedures List.
- 28) Add 33211-33212, 33214-33215, 33218-33219 to line 308
- 29) Add 31580 to line 14. Remove 31580 from line 214
- 30) Add 31582, 31587, and 31588 to line 49

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**Topic: ICD-10 Review Family Medicine**

**Discussion:** Smits introduced a summary document with suggested changes to the List from the Family Medicine review group. There were no significant suggestions and no discussion.

**Action:**

- 1) No significant changes recommended

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**Topic: ICD-10 Review Nephrology**

**Discussion:** Smits introduced a summary document with suggested changes to the nephrology lines base on the ICD-10 review. There was no discussion.

**Actions:**

- 1) Delete line 352 ACUTE GLOMERULONEPHRITIS AND OTHER ACUTE RENAL FAILURE, move all acute kidney injury codes to line 138 as renamed below and all chronic kidney disease codes to line 366 as renamed below. [Note: when lines 138 and 352 were proposed for merging, the new line scored out to place at 138]
- 2) Rename Line 138 ~~ACUTE GLOMERULONEPHRITIS: WITH LESION OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS~~ ACUTE KIDNEY INJURY
- 3) Rename Line 366 ~~NEPHROTIC SYNDROME AND OTHER RENAL DISORDERS~~ CHRONIC KIDNEY DISEASE
- 4) Move all codes that do not specify end stage renal disease from line 66 to line 366 and renamed line 366 as above

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**Topic: ICD-10 review--Vascular Surgery**

**Discussion:** Smits introduced a summary document with suggested changes to the Vascular Surgery lines base on the ICD-10 review. There was no discussion.

**Actions:**

- 1) Delete line 350 ARTERIAL ANEURYSM OF NECK. All ICD-10 codes on line 350 also appear on line 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE and will remain there. Move all CPT codes from 350 to 349.
- 2) Rename 250 ~~PERIPHERAL VASCULAR DISEASE, LIMB THREATENING~~ LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS
- 3) Rename 378 ~~ATHEROSCLEROSIS, PERIPHERAL~~ NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE
- 4) Place all peripheral vascular disease diagnoses with rest pain, ulcer, gangrene or other limb threatening conditions on upper vascular disease line (line 250)
  - a. Add to line 250: 34101-34203 (embolectomy), 35081 (repair of aneurysm), 35256 (repair of blood vessel with vein graft, lower extremity), 35450-35476 (balloon angioplasty), 35510-35671 (bypass graft), 35685, 35686, 35701-35761 (exploration of artery), 35879, 35881, 36002, 37184-37186 (thrombectomy), 37201-37209 (stenting), 37220-37235 (revascularization)
- 5) Place all non-limb threatening vascular disease diagnoses on lower vascular disease line (line 378)
  - a. Add to line 378: 24900-24931 (amputation, arm), 24935, 24940, 25900-25909 (amputation, forearm), 25915, 25920-25931 (hand amputation), 26910, 26951-2, 27025, 27290, 27295, 27590-27598 (amputation, thigh), 27880-27889 (amputation, leg), 28800-28825 (amputation, foot)
- 6) Remove all non-major blood vessels (vessels of the foot) from line 86 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES as these vessels only require suture/ligation, not repair. Add these ICD-9 codes to line 216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
  - a. S95.001A-S95.999A (laceration, specified or unspecified injury of the dorsal artery, plantar artery, dorsal vein, other specified artery of the ankle or foot, or unspecified artery of ankle or foot). Podiatry has reviewed this recommendation and concurs

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**Topic: ICD-10 review--Gastroenterology**

**Discussion:** Smits introduced a summary document with suggested changes to the gastroenterology lines base on the ICD-10 review. There was minimal discussion.

**Actions:**

- 1) Merge line 224 ESOPHAGEAL VARICES with line 62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE. Add all CPT codes on line 224 that do not appear on line 62 to line 62
- 2) Rename line 163, ACUTE VASCULAR INSUFFICIENCY OF INTESTINE
- 3) Move I84.6 (Gastric varices) from Excluded List to line 62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
- 4) Move K57.11, K57.31, K57.51, K57.91 (Diverticulosis of small and/or large intestine with bleeding) to line 62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE from line 191 DIVERTICULITIS OF COLON
- 5) Move Z80.0 (Family history of malignant neoplasm of digestive organs) from the Excluded File to line 173 ANAL, RECTAL AND COLONIC POLYPS to allow for additional screening procedures, etc

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**Topic: ICD-10 review--Urology**

**Discussion:** Smits introduced a summary document with suggested changes to the urology lines on the Prioritized List based on ICD-10 review. There was some discussion about the creation of a new guideline allowing coverage of treatment of certain benign neoplasms of the urinary organs. Olson felt that the diagnosis codes for these benign tumors should be added to line 228, and kept on line 538, with the guideline referring to both lines to clarify in what cases these diagnoses are covered. Staff will work with experts to find the correct ICD-10 codes to move to line 228.

The recommendation to rescore line 538 Condition: BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS down to line 570 was rejected as it did not fulfill the intention of the expert reviewers.

The recommendation to swap line 570 SUBLINGUAL, SCROTAL, AND PELVIC VARICES with line 579 CHRONIC PROSTATITIS, OTHER DISORDERS OF PROSTATE was not accepted. Instead, the subcommittee rescored line 579, changing the effectiveness score from 1 to 2, which increased the line score to 120 and moving the line to approximately line 550. This should have the desired outcome of making prostatitis a higher priority condition than scrotal and pelvic varices.

**Actions:**

- 1) Delete line 294 RUPTURE OF BLADDER, NONTRAUMATIC and place only ICD-10 code (N32.89 Other specified disorders of bladder) on line 690 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. Move all CPT codes from line 294 to line 690
- 2) Delete line 353 VESICULAR FISTULA and move the 2 ICD-10 codes (N32.1 Vesicointestinal fistula and N32.2 Vesical fistula, not elsewhere classified) to line 245 URINARY FISTULA. Move all CPT codes from line 353 to line 245
- 3) Add a guideline to lines 228 and 538 as shown in Attachment A
- 4) Staff to work with experts to identify ICD-10 codes to add to line 228 to represent the diagnoses specified in this guideline note
- 5) Line 570: Condition: SUBLINGUAL, SCROTAL, AND PELVIC VARICES rescored to approximately line 550

- 6) A guideline was added to line 30 as shown in Attachment A
- 7) Change treatment description of line 30 to VESICoureTERAL REFLUX  
Treatment: MEDICAL THERAPY, ~~REIMPLANTATION SURGERY~~
- 8) Change name of Line 96 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM
- 9) Line 96 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM: many diagnoses moved to line 690 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY, as there is no therapy available. These diagnoses include many congenital anomalies such as absence, aplasia, or hypoplasia of genitourinary organs
- 10) N43.3 (Hydrocele, unspecified) appears on line 567 HYDROCELE; should also appear on line 175 COMPLICATED HERNIAS (OTHER THAN DIAPHRAGMATIC HERNIA); UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE for children only, with the current guideline applying

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**Topic: ICD-10 Review—Allergy**

**Discussion:** Livingston introduced a summary document outlining the changes suggested during the expert review of the allergy lines as part of the ICD-10 conversion process. The subcommittee accepted most of the suggested changes. The committee members decided **not** to accept the recommendation of moving L27.0 Generalized skin eruption due to drugs and medicaments taken internally to the complications line, because of the unintended consequences. It will remain the lower non-funded line (Line 594).

**Actions:**

1) Split Angioedema (Line 343) into 2 new lines, one is HEREDITARY ANGIOEDEMA and the other line is ANGIOEDEMA.

a. Ranking for HEREDITARY ANGIOEDEMA

Category 6

Impact on healthy life years 8

Vulnerable populations 0

Population effects 0

Impact on healthy life years 8

Impact on pain/suffering 3

Tertiary prevention – 0

Effectiveness of treatment – 4

Need for medical service 1

Net cost 1

**Score is 1760 which is Line 166**

b. Ranking for ANGIOEDEMA

Category 7

Impact on healthy life years 3

Vulnerable populations 0

Population effects 0

Impact on pain/suffering 1

Tertiary prevention 0

Effectiveness of treatment 4

Need for medical service 1

Net cost 4  
**Score 160, Line 520**

2) Split out allergic bronchopulmonary aspergillosis from Line 354 COCCIDIOIDOMYCOSIS, HISTOPLASMOSIS, BLASTOMYCOTIC INFECTION, OPPORTUNISTIC AND OTHER MYCOSES). This is an allergic issue, not an opportunistic infection issue. Can prevent bronchiectasis if treated, long term prednisone.

c. Rescoring recommendations for new line ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ICD 10 code B44.81)

Category 7  
Impact on healthy life years 4  
Pain and suffering 2  
Vulnerable 0  
Contagion 0  
Tertiary prevention 2  
Effectiveness of treatment 4  
Need for service 1  
Net cost 3

**Score 640, Line 390**

3) Place Z01.82 Encounter for allergy testing (Currently located on the DMAP Ancillary File) on the Excluded List.

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### **Topic: ICD-10 Review—Heart and Lung Transplant**

**Discussion:** Livingston introduced a summary document outlining the changes suggested during the expert review of the heart and lung transplant lines as part of the ICD-10 conversion process. The recommendations were accepted to remove the penultimate diagnoses from the cardiac transplant lines, so only the final qualifying cardiac diagnoses remain on these lines (malignant arrhythmia, congestive heart failure, intractable angina, or myocarditis).

**Actions:**

- 1) Modify Guideline Note 70 re: heart-kidney transplants (Attachment A)
- 2) Rename Line 279 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE TRANSPOSITION OF GREAT VESSELS, HYPOPLASTIC LEFT HEART SYNDROME
- 3) Add malignant arrhythmia codes to Line 279 (I47.2 Ventricular tachycardia, I49.01 Ventricular fibrillation, I49.02 Ventricular flutter)
- 4) Add stage V and VI kidney disease to the heart-kidney transplant line 279.
- 5) Remove the following codes from 256, as these are penultimate diseases and not the terminal diagnosis leading to transplant.
  - Q20.0 Common arterial trunk 139,256
  - Q21.0 Ventricular septal defect 74,256
  - Q21.1 Atrial septal defect 129,256
  - Q25.0 Patent ductus arteriosus 85,256(D)
  - Q26.2 Total anomalous pulmonary venous connection 141,256(A)

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**Topic: ICD-10 Review—Pediatric Surgery**

**Discussion:** Smits introduced a summary document outlining the changes suggested during the expert review of the allergy lines as part of the ICD-10 conversion process. Two new lines were created and scored; the subcommittee agreed with these new lines and the scoring. However, Olson suggested that line 111 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION be rescored once the conditions in this line that were suggested for moving to the new line OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM are moved. Staff will contact expert for advice on rescoring. the Subcommittee only wants this topic brought back if the new line falls below the funding line.

Line XXX FOREIGN BODY IN GASTROINTESTINAL TRACT

Treatment: Medical therapy

ICD-10: T18.2xxA, T18.3xxA, T18.4xxA, T18.5xxA, T18.8xxA, T18.9xxA

CPT: 43247, 44363, 44383, 44390, 45307, 45332, 45378, 45379, 45915, 46608, 98966-98969, 99051, 99060, 99070, 99078, 99201-99217, 99241-99245, 99341-99366, 99441-99444

Ranking recommendations for Foreign Body in GI Tract

Category 7

Impact on healthy life years – 4

Vulnerable populations 0

Population effects 0

Impact on healthy life years 5

Impact on pain/suffering 1

Tertiary prevention – 0

Effectiveness of treatment – 5

Need for medical service 0.2

Net cost 3

**Score is 240 which is in the low 400s**

Line XXX

Condition: OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM

Treatment: MEDICAL AND SURGICAL TREATMENT

ICD-10: Q79.0-Q79.59

CPT: 39503,39545,49600-49611,51500,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99444,99468-99480,99605-99607

Ranking recommendations for OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM

Category 6

Impact on healthy life years –10

Vulnerable populations 0

Population effects 0

Impact on healthy life years 5  
Impact on pain/suffering 5  
Tertiary prevention – 5  
Effectiveness of treatment – 4  
Need for medical service 1  
Net cost 0

**Scored around line 40.**

A new line was proposed to include non-congenital neonatal conditions. This line was approved in concept. HERC staff to contact neonatology experts to approve line and score it. The subcommittee would like this topic brought back if there are issues with line scoring or if the neonatal experts disagree with the line creation or major aspects of the new line.

Line XXX  
Condition: PERINATAL GASTROINTESTINAL CONDITIONS  
Treatment: Medical therapy  
ICD-10: P78.2, P78.3, P78.82, P78.83, P78.89, P78.9  
CPT: TBD  
Ranking: TBD

There was discussion about the proposal to combine three lines (204 CONGENITAL CYSTIC LUNG - MILD AND MODERATE, line 301 HYPOPLASIA AND DYSPLASIA OF LUNG, and line 677 CONGENITAL CYSTIC LUNG – SEVERE). Dodson wanted to know what the evidence was around the effectiveness of treatment of severe congenital cystic lung. Coffman noted that there was no distinction in the ICD-9 or ICD-10 codes for this condition (the only treatment distinction was noted in the line names). Nothing currently prevents treatment of severe cystic lung in the DMAP system. Dodson was then fine with the combining of these lines.

Line 204  
Condition: CONGENITAL LUNG ANOMALIES  
Treatment: MEDICAL AND SURGICAL TREATMENT  
ICD-10: J98.4, Q33.0, Q33.2, Q33.3, Q33.4, Q33.6  
CPT: 31601,31603,31820,31825,32140,32141,32480-32488,32500,32501,32662,32800,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99444,99468-99480,99605-99607  
HCPCS: G0406-G0408,G0425-G0427,S0270-S0274

There was some discussion about the proposal to rescore line 40 SPINA BIFIDA. The group thought that perhaps the medical and surgical treatments for this condition should be separated. HERC staff was directed to discuss this with neurosurgical and possibly neonatal experts.

**Actions:**

- 1) New line created for FOREIGN BODY IN GASTROINTESTINAL TRACT and scored to a line in the low 400s
- 2) New line created for OTHER CONGENITAL ANOMALIES OF MUSCULOSKELETAL SYSTEM and scored to approximately line 40

- 3) HERC staff to work with gastroenterology experts to rescore line 111 once proposed diagnosis movement to new line has occurred
- 4) HERC staff to work with neonatal experts to create and score a new line concerning neonatal gastrointestinal conditions
- 5) Combine line 204 CONGENITAL CYSTIC LUNG - MILD AND MODERATE, line 301 HYPOPLASIA AND DYSPLASIA OF LUNG, and line 677 CONGENITAL CYSTIC LUNG - SEVERE. Rename "Congenital lung anomalies"
- 6) HERC staff to consult neurosurgery and possibly neonatology regarding scoring line 40 SPINA BIFIDA
- 7) Rename Line 444 INCONTINENCE OF FECES; FECAL IMPACTION
- 8) Move K56.41 (Fecal impaction) from line 48 INTUSSUSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, AND FOREIGN BODY IN STOMACH, INTESTINES, COLON, AND RECTUM to line 444 and rename line 444 INCONTINENCE OF FECES; FECAL IMPACTION as noted above
- 9) Meconium diagnoses (P24) deleted from line 111 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION and left on other lines (not a congenital issue)

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**Topic: Vascular bone grafts for avascular necrosis of the hip**

**Discussion:** This topic was deferred to the April VbBS meeting due to lack of availability of experts to testify at the current meeting.

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**Topic: Continuous glucose monitoring**

**Discussion:** Smits introduced a summary document outlining proposed changes to the coverage for continuous glucose monitoring (CGM). New written testimony from the American Diabetes Association was distributed to the subcommittee members. Olson did not feel that the evidence supported the use of CGM. He wondered if in the few cases in which hypoglycemia is a recurrent problem that this device might be covered through the exceptions process. Kirk thought this would probably be the case. Dodson agreed that the science does not support the use of CGM, but that the group could review this topic again if new evidence is produced. Pollack agreed that CGM appeared to be a poor return on investment for OHP. The decision was to remove the procedure codes for CGM from the List.

**Actions:**

- 1) Remove continuous glucose monitoring (CPT 95250-1) from line 10 TYPE I DIABETES MELLITUS

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**Topic: Gender identity disorder**

**Discussion:** Smits introduced a summary document outlining proposed addition of coverage for gender identity disorder. Several experts from advocacy groups gave public testimony and answered the member's questions.

The group agreed with the proposal to split the current line Line 513 GENDER IDENTIFICATION DISORDER, PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS into two separate lines. The new Gender Dysphoria line was rescored as shown

below. The major discussion during the rescoring was about the level of vulnerability of this population. The major scoring weights were determined based on the evidence of improved outcomes for patients who had puberty suppression.

Reranking:  
Gender ID disorder  
Category: 7  
HLY: 3  
Suffering: 4  
Population effects: 0  
Vulnerability: 0  
Tertiary prevention: 3  
Effectiveness: 2  
Need for service: 1  
Net cost: 2  
Score: 400  
Rank: line 430 approximately

The line containing paraphilias was not rescored due to time constraints. The subcommittee directed HERC staff to work with Dr. Pollack (the mental health representative on the VbBS) to create a proposed ranking which will then be sent to members for approval. This topic will be brought back in April for final approval.

The new guideline restricting the types of treatments for gender dysphoria was discussed in detail. The experts testifying before the subcommittee recommended that puberty suppressing medications be limited to children who have attained at least Tanner stage 2 in sexual development, as children in Tanner stage 1 have not yet started puberty. The treatment should be allowed through Tanner stage 5 to allow for different stages of puberty.

Heidi Allen summarized the previously presented literature on the harms of not treating transgendered children during puberty. Tyack asked if there is evidence of the safety of these medications, to which the experts replied that there was. Pollack noted that the likelihood of misdiagnosis is very rare, and the use of puberty suppressing medication was not subject to abuse. Ocker asked the experts who provided care for these patients. The response was psychiatry, in conjunction with endocrinology and primary care. Kirk had concerns for access to appropriate care outside of Portland metro area. The experts indicated that resources are available throughout the state. Pollack reviewed DSM5 criteria for gender identity disorder, which has fairly restrictive diagnostic criteria. The group decided that there was evidence of effectiveness for treatment of adolescents with gender identity disorder and no evidence of harms. This treatment was specified as being included on this line with a guideline.

**Actions:**

- 1) Divide Line 513 GENDER IDENTIFICATION DISORDER, PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS into two separate lines
  - a. Line ~~XXX GENDER IDENTIFICATION DISORDER~~ DYSPHORIA was scored to approximately line 430

- b. Line XXX PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS scoring was not completed. HERC staff will work with Dr. Pollack to prepare a proposed line scoring, which will then be voted on by the group via email.
- 2) Add histrelin (Supprelin) insertion (GnRH analog used to suppress puberty) CPT (11981-11983) codes to new gender dysphoria line and alter existing guideline to include this line
- 3) Adopt the guideline as shown in Attachment B for the Gender Dysphoria line
- 4) The new guideline regarding implantable GNRH analog therapy was modified to include the new Gender Dysphoria line

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**Topic: HPV vaccination for males**

**Discussion:** Smits introduced a summary document outlining the proposed addition of coverage of HPV vaccination for males to the Prevention Tables. Olson noted that the Commission should follow ACIP recommendations, which are evidence based. He recommended increasing coverage for both males and females to age 26 (instead of the proposed 18) to be consistent with current ACIP guidelines. He felt that the vaccine should be covered for boys to both reduce the risk of head and neck cancer and to reduce the size of the viral pool for girls. Dodson agreed that the age for coverage should be increased to 26; she felt that the cut-off at age 18 was financially based, not evidence based. Bickle noted that DMAP recommends following ACIP. Current DMAP administrative rules requires following ACIP which conflicts with the current List coverage of HPV vaccine. Kirk noted that several medical directors are opposed to vaccinate over age 18, but he also agreed to increase coverage to age 26.

**Actions:**

- 1) Change the footnotes of the Prevention tables for Ages Birth to 10 and ages 11 to 24 -- Interventions for the General Population to read "HPV2 and HPV4 for ~~women~~ females aged 9 to ~~18~~ 26. ~~Discussion with provider regarding HPV4 for males aged 9 through 18~~ 26."

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**Topic: Lichen sclerosis**

**Discussion:** Smits introduced a summary document outlining the proposed addition of coverage for lichen sclerosis. Olson noted that the main intervention in the treatment of this condition was examinations, and there was a low potential for overuse of the medical system for treatment of this condition. Smits noted that possible treatments for this condition which would be covered if this condition was moved to a covered area of the List were topical medications, biopsies, and exams.

**Actions:**

- 1) Add 701.0 to line 460 DYSTROPHY OF VULVA; keep on line 534 CIRCUMSCRIBED SCLERODERMA
- 2) Add the following coding specification to line 460
  - a. "ICD-9 701.0 is included on this line only for the diagnosis of lichen sclerosis."

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**Topic: Re-ranking the esophagitis line**

**Discussion:** Livingston introduced a summary document outlining a proposed re-ranking of the esophagitis line. There was some discussion about the current ranking and the frequency of use of PPI medications. There was clarification that diagnostic endoscopy for those with worrisome dysphagia would be covered as usual in the diagnostic file. And a upcoming guideline on upper endoscopy is forthcoming.

**Actions:**

- 1) Change the following scores for Line 423 Esophagitis to Healthy Life Years to 3  
Effectiveness 3  
Need for Services 0.3  
Results in a score of 126  
Approximate New Line: 540

---

**Topic: Tympanostomy tubes for chronic otitis media and hearing loss guideline**

**Discussion:** Livingston introduced a summary document outlining suggested changes to the coverage of tympanostomy tubes. Evidence was reviewed indicating that current ranking of 502 CHRONIC OTITIS MEDIA is still consistent with the evidence. There was a discussion of options of enabling certain cases of chronic otitis media to be covered in certain special cases; however, there is no evidence suggesting these subgroups benefit specifically, at at this time insufficient evidence supports making an exception for the List.

**Actions:**

- 1) Clarify intent (for Medical Directors and DMAP purposes) that until changes go into effect on October 1, 2012, the HERC intent is for Guideline Note 51, to provide parameters for tympanostomy tubes on Line 383 HEARING LOSS - AGE 5 OR UNDER
- 2) For the October 1, 2012 Prioritized List, the following change was made to Line 383
  - a. Remove CPT code 69436
  - b. Remove coding specification "CPT Code 69436 is included on this line only as treatment for conductive hearing loss (389.0,389.2)"

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**Public Comment**

No public testimony was received except as noted in topic sections above.

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**Issues for next meeting:**

- 1) Vascular bone grafts for avascular necrosis of the hip
- 2) Scoring of new paraphilias line
- 3) ICD-10 review for Podiatry, Dermatology, Infectious Disease, Sports Medicine, Oral Maxillofacial surgery, and Otolaryngology

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**Next meeting:** April 12, 2012 at Meridian Park Hospital in Tualatin, OR.

## Attachment A

### Guideline Changes as Part of the ICD-10 and/or Biennial Review

**Note: these take effect with the next Biennial Review List (October 1, 2013 or later)**

## New Guidelines

### **GUIDELINE NOTE XXX TREATMENT OF BENIGN NEOPLASM OF URINARY ORGANS**

*Line 228, 538*

Treatment of benign urinary system tumors is covered with evidence of bleeding or urinary obstruction. Treatment of 1) oncocytoma which is >5 cm in size or symptomatic and 2) angiomyolipoma (AML) which is >5cm in women of child bearing age or in symptomatic men or women is covered.

### **GUIDELINE NOTE XXX OBSTRUCTIVE AND REFLEX UROPATHY**

*Line 30*

ICD-10 N13.9 (Obstructive and reflux uropathy unspecified) appears on this line for pediatric populations only

### **GUIDELINE XXX GENDER DYSPHORIA**

*Line XXX*

Hormone treatment is included on this line only for use in delaying the onset of puberty and/or continued pubertal development for gender questioning children and adolescents (age 17 and younger) at Tanner stage 2 and above.

## MODIFIED GUIDELINES

### **GUIDELINE NOTE XXX IMPLANTABLE GNRH ANALOG THERAPY**

*Line 193,XXX*

Use of drug delivery implant therapy for GnRH analogue therapy (such as histrelin) (CPT 11981-11983) is covered only after injectable depot medications (such as Lupron) have been tried or are contraindicated.

### **GUIDELINE NOTE 70, HEART-KIDNEY TRANSPLANTS**

*Line 279*

Patients under consideration for heart/kidney transplant must qualify for each individual type of transplant under current DMAP administrative rules and transplant center criteria with the exception of any exclusions due to heart and/or kidney disease. Qualifying renal disease is limited to Stage V or VI.

## **Section 2**

### **ICD-10 Mapping**

# Overview of Recommendations for Converting Lines to ICD-10-CM Podiatry

*Specialty consultants: Dr. Andrew Schink; Dr. Clifford Mah; Dr. Chris Seufferling*

**CREATE NEW LINES:** none

**COMBINE MULTIPLE LINES:** none

**DELETE LINES:** none

**RESCORE LINES:** none

## **GUIDELINES/CODE PLACEMENT CHANGES**

- 1) Add coverage for high risk patients for certain currently uncovered diagnoses of foot conditions to a covered line, with a guideline.
  - a. Add M20.1x (Hallux vulgus (acquired)—i.e.bunion), M20.3x (Hallux varus (acquired)), M20.4x (other hammer toes, acquired), M92.6x and M92.7x (juvenile osteochondrosis, ankle/foot), and L84 (corns and callosities) to line 172 PREVENTIVE FOOT CARE and keep on line 565 DEFORMITIES OF FOOT or 618 CORNS AND CALLUSES with a guideline as noted below
    - i. Add CPT codes 11055-11057 (paring or cutting of benign hyperkeratotic lesion) to line 172 to allow treatment of corns and calluses
    - ii. Add CPT codes 27612,27690-27692,28100-28011,28050-28054, 28070-28072,28086-28092,28110-28124,28126-28160,28200-28315, 28340-28341,28360,28705-28760,29750 to line 172 to allow treatment of hallus vulgus and varus, and hammer toes. These are surgical repair codes.
    - iii. Add office visit CPT codes 98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99444,99468-99480,99605-99607 to line 172
    - iv. Note: line 172 currently has only a very limited set of CPT codes involving nail care
  - b. Create a new guideline allowing coverage of certain diagnoses for patients at high risk of developing foot ulcers

## **GUIDELINE XXX PODIATRIC PROCEDURES FOR PATIENTS AT HIGH RISK FOR DEVELOPING FOOT ULCERS**

*Lines: 172, 565, 618*

ICD-10 codes M20.1x [hallux valgus (acquired)], M20.3x [Hallux varus (acquired)], M20.4x (other hammer toes, acquired), M92.6x and M92.7x (juvenile osteochondrosis, ankle/foot), and L84 (corns and callosities) are included on line 172 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS only for patients at high risk of developing foot ulcers, defined as patients with 1) diabetes, 2) peripheral vascular disease, 3) peripheral neuropathy or 4) history of foot ulcer. For non-high risk patients, these diagnoses are located on lines 565 DEFORMITIES OF FOOT or 618 CORNS AND CALLUSES.

- 2) Allow coverage of certain bone fusion and osteotomies for tendon tears and ruptures. This would require code movement and the creation of a coding specification

# Overview of Recommendations for Converting Lines to ICD-10-CM

## Podiatry

- a. Add CPT codes 28705-28760, 29890-29907 to lines 406 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, GRADE II AND III and 531 PERIPHERAL ENTHEOSOPATHIES
  - i. These CPT codes represent ankle arthrodesis and arthroscopy procedures
  - ii. The ICD-10 codes noted below are already on lines 406 or 531
- b. Add a coding specification to lines 406 and 531 as below
  - i. "CPT codes 28705-28760, 29890-29907 are included in this line only for the treatment of tibial and peroneal tendonitis, and tendon tears or ruptures of the ankle (ICD-10 codes M66.27x, M66.37x, M66.87x, M76.7x, M76.80, M76.86x, S86.01xx, S93.49xx, S96.01xx, S96.11xx, S96.21xx, S96.81xx, and S96.91xx)."
    1. Note: these ICD-10 codes represent anterior and posterior tibial tendonitis, spontaneous rupture of tendons of ankle, peroneal tendinitis, tendon sprains and strains at ankle level)

**RENAME LINES:** none

### OTHER CODE PLACEMENT

- 1) Move M20.2x (hallux rigidus) and M24.671-3 (Ankylosis, ankle) from line 565 DEFORMITIES OF FOOT to line 489 OSTEOARTHRITIS AND ALLIED DISORDERS, as these conditions are equivalent to arthritis
  - a. Add CPT codes 20920-20924,27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28341,28360,28705-28760,29450,29750,29904-29907 to line 489 to allow treatment of hallux rigidus
- 2) Move M24.17x (Other articular cartilage disorders, ankle/foot) from line 565 DEFORMITIES OF FOOT to line 455 INTERNAL DERANGEMENT OF KNEE AND LIGAMENOUS DISRUPTIONS OF THE KNEE, GRADE II AND III as this condition is of equivalent severity
  - a. Add CPT codes 20920-20924,27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28341,28360,28705-28760,29450,29750,29891-29907 to line 455 to allow treatment of other cartilage disorders
- 3) Move Q66.1 (Congenital talipes calcaneovarus), Q66.3 (Other congenital varus deformities of feet), and Q66.6 (Other congenital valgus deformities of feet) from line 565 DEFORMITIES OF FOOT to line 297 DEFORMITY/CLOSED DISLOCATION OF JOINT as these are equivalent to "club foot, congenital" which is contained on this line, and appropriate treatment CPT codes are present on this line.

# Overview of Recommendations for Converting Lines to ICD-10-CM Podiatry

## Appendix A: Podiatry changes for earlier implementation in ICD-9

### GUIDELINES/CODE PLACEMENT CHANGES

- 1) Add coverage for high risk patients for certain currently uncovered diagnoses of foot conditions to a covered line, with a guideline.
  - a. Add 727.1 (Hallux vulgaris (acquired)—i.e. bunion), 735.1 (Hallux varus (acquired)), 735.4 (other hammer toes, acquired), 732.4 and 732.5 (juvenile osteochondrosis, ankle/foot), and 700 (corns and callosities) to line 172 PREVENTIVE FOOT CARE and keep on line 565 DEFORMITIES OF FOOT or 618 CORNS AND CALLUSES with a guideline as noted below
    - i. Add CPT codes 11055-11057 (paring or cutting of benign hyperkeratotic lesion) to line 172 to allow treatment of corns and calluses
    - ii. Add CPT codes 27612,27690-27692,28100-28011,28050-28054, 28070-28072,28086-28092,28110-28124,28126-28160,28200-28315, 28340-28341,28360,28705-28760,29750 to line 172 to allow treatment of hallus vulgaris and varus, and hammer toes. These are surgical repair codes.
    - iii. Add office visit CPT codes 98966-98969, 99051,99060, 99070,99078, 99201-99360,99366,99374,99375,99379-99444,99468-99480,99605-99607 to line 172
    - iv. Note: line 172 currently has only a very limited set of CPT codes involving nail care
  - b. Create a new guideline allowing coverage of certain diagnoses for patients at high risk of developing foot ulcers

### GUIDELINE XXX PODIATRIC PROCEDURES FOR PATIENTS AT HIGH RISK FOR DEVELOPING FOOT ULCERS

*Lines: 172, 565, 618*

ICD-9/10 codes 727.1/M20.1x [hallux valgus (acquired)], 735.1/M20.3x [Hallux varus (acquired)], 735.4 /M20.4x (other hammer toes, acquired), 732.4 and 732.5/M92.6x and M92.7x (juvenile osteochondrosis, ankle/foot), and 700/L84 (corns and callosities) are included on line 172 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS only for patients at high risk of developing foot ulcers, defined as patients with 1) diabetes, 2) peripheral vascular disease, 3) peripheral neuropathy or 4) history of foot ulcer. For non-high risk patients, these diagnoses are located on lines 565 DEFORMITIES OF FOOT or 618 CORNS AND CALLUSES.

- 2) Allow coverage of certain bone fusion and osteotomies for tendon tears and ruptures. This would require code movement and the creation of a coding specification
  - a. Add CPT codes 28705-28760, 29890-29907 to lines 406 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, GRADE II AND III and 531 PERIPHERAL ENTHERSOPATHIES
    - i. These CPT codes represent ankle arthrodesis and arthroscopy procedures
    - ii. The ICD-9 codes noted below are currently on lines 406 or 531
  - b. Add a coding specification to lines 406 and 531 as below
    - i. "CPT codes 28705-28760, 29890-29907 are included in this line only for the treatment of tibial and peroneal tendonitis, and tendon tears or ruptures of the ankle (ICD-9 codes 726.72, 726.79, 727.68, 845.0)."
      1. Note: these ICD-10 codes represent anterior and posterior tibial tendonitis, spontaneous rupture of tendons of ankle, peroneal tendinitis, tendon sprains and strains at ankle level)

# Overview of Recommendations for Converting Lines to ICD-10-CM Podiatry

## OTHER CODE PLACEMENT

- 1) Move 735.2 (hallux rigidus) and 718.57 (Ankylosis, ankle) from line 565 DEFORMITIES OF FOOT to line 489 OSTEOARTHRITIS AND ALLIED DISORDERS, as these conditions are equivalent to arthritis
  - a. Add CPT codes 20920-20924,27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28341,28360,28705-28760,29450,29750,29904-29907 to line 489 to allow treatment of hallux rigidus
- 2) Move 718.07 (Other articular cartilage disorders, ankle/foot) from line 565 DEFORMITIES OF FOOT to line 455 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, GRADE II AND III as this condition is of equivalent severity
  - a. Add CPT codes 20920-20924,27612,27690-27692,28008,28010,28035,28050-28072,28086-28092,28110-28119,28126-28160,28220-28341,28360,28705-28760,29450,29750,29891-29907 to line 455 to allow treatment of other cartilage disorders
- 3) Move 754.50 (Talipes varus), 754.59 (Congenital talipes calcaneovarus), 754.60 (talipes valgus), and 754.69 (Other congenital valgus deformities of feet) from line 565 DEFORMITIES OF FOOT to line 297 DEFORMITY/CLOSED DISLOCATION OF JOINT as these are equivalent to “club foot, congenital” which is contained on this line, and appropriate treatment CPT codes are present on this line.
  - a. Note: 754.51-3 (Talipes equinovarus, Metatarsus primus varus, Metatarsus varus) are currently on line 297 DEFORMITY/CLOSED DISLOCATION OF JOINT
  - b. Note: 754.61 (Congenital pes planus) is currently on line 550 DEFORMITIES OF UPPER BODY AND ALL LIMBS; 754.62 (Talipes calcaneovalgus) is currently on line 297 DEFORMITY/CLOSED DISLOCATION OF JOINT

# Dermatology Recommendations for ICD-10

Specialty consultants: Tavelli, Baker, and Simpson

## CREATE NEW LINES

### 1) MODERATE/SEVERE INFLAMMATORY SKIN DISEASE

Moderate to severe ~~psoriasis~~ [inflammatory skin disease](#) is defined as having functional impairment and one or more of the following:

1. At least 10% of body surface area involved; and/or,
2. Hand, foot or mucous membrane involvement.

First line agents include topical agents, oral retinoids, phototherapy and methotrexate. Use of other systemic agents should be limited to those who fail, have contraindications to, ~~or do not have access to~~ first line agents. [Biologics are only covered for moderate/severe psoriasis after documented failure of first line agents and second line agents.](#)

**Ranking recommendations:** (moderate severe psoriasis used to be 134 (was with pyoderma)

Category 7

Impact on Healthy Life Years 3 – QOL, these people suffer badly, affects what they do every day, disabling/disfiguring, if have psoriasis on palms/soles, can't work at all

Impact on pain and suffering 3

Population effects 0

Vulnerable populations 0

Tertiary prevention 0

Effectiveness 3

Need for treatment 0.9

Net cost 2

Score 324 which is Line 450

### 2) ACNE CONGLOBATA (SEVERE CYSTIC ACNE) (derived from line 545 Cystic Acne)

- a. Includes acne conglobata only, no other codes
- b. Adopt a guideline to define severe

Category 7.

Impact on Healthy Life Years 2

Impact on Pain and Suffering 3

Population effects 0

Vulnerable populations 0

Tertiary prevention 2 (high likelihood of decrease permanent disfigurement/scarring; possible decrease in suicide risk)

Effectiveness 4

Need for treatment 1

Net cost 3

SCORE 560, PUTS ON LINE 410

## Dermatology Recommendations for ICD-10

### 3) HYDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP

Both of these conditions are very resistant to treatment. The severity may be reduced with oral isotretinoin, antibiotics, dapsone, and injected or systemic steroids.

*Category 7.*

*Impact on Healthy Life Years 2*

*Impact on Pain and Suffering 3*

*Population effects 0*

*Vulnerable populations 0*

*Tertiary prevention 1 (decreases risk of scarring down axilla; abscesses; but surgery end stage decision, cure, but 50% graft entire axilla and get disease around graft)*

*Effectiveness 1*

*Need for treatment 1*

*Net cost 4*

*SCORE 120 , PUTS ON LINE 550*

### 4) HEMANGIOMAS, COMPLICATED

Hemangiomas are covered on this line when they are ulcerated, infected, recurrently hemorrhaging, or function-threatening (e.g. eyelid hemangioma).

TREATMENT: MEDICAL THERAPY

*Category 7*

*Impact on Healthy Life Years 5*

*Impact on Pain and Suffering 2*

*Population effects 0*

*Vulnerable populations 0*

*Tertiary prevention 5*

*Effectiveness 4*

*Need for treatment 1*

*Net cost 3*

*SCORE 960 , PUTS ON LINE 350*

### 5) ACTINIC KERATOSIS (was on 655 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES), only has L57.0 Actinic Keratosis. Should be its own line 5-8% become squamous cell carcinoma, not quite premalignant line.

*Category 7.*

*Impact on Healthy Life Years 1*

*Impact on Pain and Suffering 0*

*Population effects 0*

*Vulnerable populations 0*

*Tertiary prevention 2*

*Effectiveness 3*

*Need for treatment 0.6*

*Net cost 4*

*SCORE 108 , PUTS ON LINE 553*

# Dermatology Recommendations for ICD-10

## DELETE LINES

134 PYODERMA; MODERATE/SEVERE PSORIASIS MEDICAL THERAPY  
Pyoderma codes move to cellulitis line 214. Psoriasis divided into mild and moderate/severe disease

573 Xerosis, moving single code to 688

603 Erythema Multiforme Minor, codes moving 530 Erythematous Conditions line

## RESCORE LINES

- 1) 225 TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM needs to be ranked higher, life threatening  
*Category 6*  
*Impact on Healthy Life Years 9*  
*Impact on Pain and Suffering 5*  
*Population effects 0*  
*Vulnerable populations 0*  
*Tertiary prevention 2*  
*Effectiveness 3*  
*Need for treatment 1*  
*Net cost 1*  
*SCORE 1920, PUTS around LINE 160*

## GUIDELINES

Delete current moderate/severe psoriasis guideline to New moderate/severe inflammatory skin disease guideline as above.

## RENAME LINES

- 1) 530 TOXIC ERYTHEMA, ACNE ROSACEA, DISCOID LUPUS rename TO ERYTHEMATOUS CONDITIONS
- 2) 545 ~~CYSTIC ACNE~~ ACNE; ROSACEA
  - a. Moved rosacea codes from 530 to this line
  - b. Moved out hydradenitis suppurative to its own line
- 3) 566 FOREIGN BODY GRANULOMA OF MUSCLE, ~~GRANULOMA OF~~ SKIN, AND SUBCUTANEOUS TISSUE
- 4) 578 ~~KERATODERMA, ACANTHOSIS NIGRICANS, STRIAE ATROPHICAE~~, MILD ECZEMATOUS AND OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN

## CODE MOVEMENT WORTH REVIEW

### Moved to Diagnostic files

Pruritis codes (L29.8 and L29.9)  
Hirsutism (L68.0)

## **Dermatology Recommendations for ICD-10**

Move Q82.8 Other specified congenital malformations of skin to both higher severe line and 688.

New coding specification

Q82.8 is only included [on the higher line] for the diagnosis of Keratosis follicularis that meets the severity guideline criteria. Other diseases included within Q82.8 are not covered on this line.

Note to actuaries section

- 1) Would start covering severe acne
- 2) Would start covering moderate/severe psoriasis
- 3) Would cover function-threatening hemangiomas

## Lines attached to Issue: 68 ICD-10 review Dermatology

Line	Condition	Treatment
223	BULLOUS DERMATOSES OF THE SKIN	MEDICAL THERAPY
225	TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM	MEDICAL THERAPY
243	MALIGNANT MELANOMA OF SKIN	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
257	DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU	DESTRUCT/EXCISION/MEDICAL THERAPY
432	EPIDERMOLYSIS BULLOSA	MEDICAL THERAPY
512	LICHEN PLANUS	MEDICAL THERAPY
530	ERYTHEMATOUS CONDITIONS	MEDICAL THERAPY
534	CIRCUMSCRIBED SCLERODERMA	MEDICAL THERAPY
542	DISORDERS OF SWEAT GLANDS	MEDICAL THERAPY
545	CYSTIC ACNE	MEDICAL AND SURGICAL TREATMENT
553	ATOPIC DERMATITIS	MEDICAL THERAPY
554	CONTACT DERMATITIS AND OTHER ECZEMA	MEDICAL THERAPY
559	ICHTHYOSIS	MEDICAL THERAPY
564	MILD PSORIASIS ; DERMATOPHYTOSIS: SCALP, HAND, BODY, DEEP-SEATED	MEDICAL THERAPY
566	FOREIGN BODY GRANULOMA OF MUSCLE, SKIN AND SUBCUTANEOUS TISSUE	REMOVAL OF GRANULOMA
578	MILD ECZEMATOUS AND OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN	MEDICAL THERAPY
601	STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES	INCISION AND DRAINAGE, MEDICAL THERAPY
615	DISEASE OF NAILS, HAIR AND HAIR FOLLICLES	MEDICAL THERAPY

Line	Condition	Treatment
633	KELOID SCAR; OTHER ABNORMAL GRANULATION TISSUE	INTRALESIONAL INJECTIONS/DESTRUCTION/EXCISION, RADIATION THERAPY
651	SEBACEOUS CYST	MEDICAL AND SURGICAL TREATMENT
652	SEBORRHEIC KERATOSIS, DYSCHROMIA, AND VASCULAR DISORDERS, SCAR CONDITIONS, AND FIBROSIS OF SKIN	MEDICAL AND SURGICAL TREATMENT
656	BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES	MEDICAL THERAPY
657	DISEASE OF CAPILLARIES	EXCISION
688	DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	EVALUATION

## Treatment Guidelines for Inflammatory Skin Disease

These guidelines were developed using some cost-effectiveness data, expert opinion, and physician preference data. A thorough systematic review of cost-effectiveness was not performed.

### Proposed Treatment Guideline for Moderate-to-Severe Psoriasis

#### First-line agents

Potent topical corticosteroids  
Narrowband UVB  
Methotrexate  
+/- cyclosporine

#### Second-line agents

Other systemic immunosuppressives: cyclosporine, mycophenolate mofetil  
Oral retinoids – acitretin or isotretinoin  
Biologics – infliximab, adalimumab, etanercept, ustekinumab, alefacept

Note: combinations of these medications are also used in certain clinical situations.

#### References

1. Hsu S, Papp KA, Lebwohl MG, Bagel J, Blauvelt A, Duffin KC, Crowley J, Eichenfield LF, Feldman SR, Fiorentino DF, Gelfand JM, Gottlieb AB, Jacobsen C, Kalb RE, Kavanaugh A, Korman NJ, Krueger GG, Michelin MA, Morison W, Ritchlin CT, Stein Gold L, Stone SP, Strober BE, Van Voorhees AS, Weiss SC, Wanat K, Bebo BF Jr; National Psoriasis Foundation Medical Board. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012 Jan;148(1):95-102.

Note: Guidelines in this paper do not specify a first-line therapy.

2. Wan J, Abuabara K, Troxel AB, Shin DB, Van Voorhees AS, Bebo BF Jr, Krueger GG, Callis Duffin K, Gelfand JM. Dermatologist preferences for first-line therapy of moderate to severe psoriasis in healthy adult patients. J Am Acad Dermatol. 2012 Mar;66(3):376-86. Epub 2011 Aug 19.

### Proposed Treatment Guideline for Moderate-to-Severe Atopic Dermatitis

The prevalence of atopic dermatitis is approximately 10% in children and possibly 1% in adults. Up to 1/3 of children may have moderate-to-severe disease. The prevalence of moderate-to-severe disease in adults is unknown. The vast majority of moderate-severe disease may be adequately controlled with topical corticosteroids, especially in children.

#### First-line agents

Topical corticosteroids  
Narrowband UVB  
Cyclosporine (1 year limit)  
Methotrexate  
Azathioprine

#### Second-line agents

Topical pimecrolimus and topical tacrolimus  
Other systemic immunosuppressives: mycophenolate mofetil  
Biologics – interferon-gamma

## Treatment Guidelines for Inflammatory Skin Disease

### References

Schmitt J, Schäkel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. Acta Derm Venereol. 2007;87(2):100-11.

This paper concluded that cyclosporine should be first-line systemic therapy for severe atopic dermatitis

### **Proposed Treatment Guideline for Moderate-to-Severe Pityriasis Rubra Pilaris**

This is a very rare self-limited severe inflammatory skin disorder that last for several years. It may affect both adults and children. The incidence is unknown but may be 1 in 5000 new visits to a dermatologist. There are no randomized controlled studies available for this rare condition. Treatment guidelines based on expert opinion and case reports.

#### First-line agents

Topical corticosteroids  
Acitretin  
Methotrexate  
Narrowband UVB

#### Second-line agents

Isotretinoin  
Other systemic immunosuppressives: azathioprine, cyclosporine  
Biologics – infliximab

### **Proposed Treatment Guideline for Moderate-to-Severe Discoid Lupus Erythematosus**

#### First-line agents

Topical corticosteroids  
Intralesional corticosteroids  
Hydroxychloroquine

#### Second-line agents

Topical tacrolimus or pimecrolimus  
Chloroquine  
Quinacrine  
Acitretin and isotretinoin  
Thalidomide  
Dapsone  
Azathioprine

### **Hemangiomas, ulcerated (usually lip or diaper area)**

#### First-line

Wound care with silvadene, zinc oxide  
Antibiotics

#### Second line

Propranolol

## Treatment Guidelines for Inflammatory Skin Disease

Vascular laser therapy  
Becaplermin topical (Regranex)

### **Hemangiomas, function threatening such as eyesight, feeding**

#### First-line

Propranolol- emerging as new first-line over steroids  
Oral corticosteroids

# Care Oregon Guidelines of Care

Bert G Tavelli, MD  
Care Oregon Guidelines Dermatology Task Force  
April, 2012

## Discoid Lupus Erythematosus—Guidelines of Care

**Rationale:** Despite the relative infrequency of internal involvement, aggressive treatment of DLE is warranted because the scarring from the disease can be devastating, including scarring alopecia, and depigmentation in dark-skinned individuals.

- Coverage for DLE requires: Widespread disease, especially on the face, ears and scalp with evidence of scarring.
- Antimalarials, singly, or in combination are the mainstay of therapy. Resistant cases may be treated with oral retinoids, systemic corticosteroids, gold, thalidomide, and other immunosuppressive agents.
- 

Discoid LE



Discoid LE



## Pityriasis Rubra Pilaris

Coverage of Pityriasis Rubra Pilaris requires:

- Typical features on clinical exam **and** histopathology
- Widespread disease involving >50% of skin /erythroderma

Oral retinoids and methotrexate constitute the mainstays of treatment

## Pityriasis Rubra Pilaris



## Pityriasis Rubra Piularis



## Moderate-to-Severe Inflammatory Skin Disease

- Similar or worse impact on quality of life compared to other chronic diseases such as COPD, CHF
- Highly treatable

## MYTH

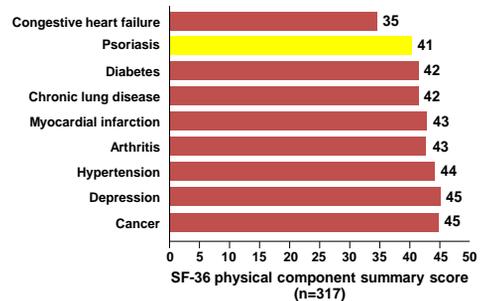
**“SKIN DISEASES LIKE ECZEMA AND PSORIASIS ARE MAINLY A COSMETIC ISSUE”**

## FACT

**THESE DISEASES HAVE A PROFOUND IMPACT ON A PATIENT’S PHYSICAL AND MENTAL WELL-BEING**

**MORE THAN MANY CHRONIC ILLNESSES**

Physical Impact of Psoriasis Compared to Other Diseases



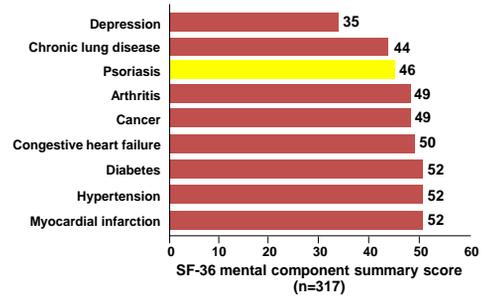
Lower scores indicate worse patient-reported outcomes.

Rapp SR, et al. *J Am Acad Dermatol.* 1999;41:401-407.

## PHYSICAL SYMPTOMS

- ITCHING
- PAIN
- BLEEDING SKIN
- INABILITY TO SLEEP COMFORTABLY
- TIME OFF WORK
- DEATH

Mental Impact of Psoriasis Compared to Other Diseases



Lower scores indicate worse patient-reported outcomes.

Rapp SR, et al. *J Am Acad Dermatol*. 1999;41:401-407.

## PROBLEM

INFLAMMATORY SKIN DISEASES HAVE A  
SPECTRUM OF SEVERITY ALL WITH THE SAME  
ICD-9/10 CODE

Examples of moderate-to-severe  
inflammatory skin disease

Atopic Dermatitis





Psoriasis



**SEVERE PSORIASIS**



## LIFE THREATENING PUSTULAR PSORIASIS



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## Pityriasis Rubra Pilaris



### Discoid lupus erythematosus



### Function-threatening hemangiomas

- Early treatment preserves function
- Treatment lasts until hemangioma involutes





### Ulcerated hemangiomas

- Painful and often infected
- Treatment lasts until hemangioma involutes





# Overview of Recommendations for Converting Lines to ICD-10-CM Sports Medicine

*Specialty consultants:* Dr. Ryan Petering, Dr. Melissa Novak, Dr. Charles Webb

## CREATE NEW LINES

Create new line for Achilles tendonitis, lateral epicondylitis, and medial epicondylitis. These conditions are currently on lines 516 and 531. They have evidence for effectiveness of treatment. There is good evidence for cortisone injections allowing better compliance with physical therapy and other treatment modalities, earlier mobilization, and quicker return to function.

Line XXX ACHILLES TENDONITIS, LATERAL AND MEDIAL  
EPICONDYLITIS

Treatment: MEDICAL AND SURGICAL THERAPY

ICD-10: M76.60-M76.62, M77.01-M77.12

CPT: from 516 and 531

Scoring:

Category: 7

IHLY: 2

IPS: 2

Pop: 0

Vuln: 0

Tertiary: 0

Effect: 4

Cost: 4

Need for treatment: 0.9

Score: 288 Approx line: 475

## COMBINE MULTIPLE LINES

None

## DELETE LINES

None

## RESCORE LINES

None

## GUIDELINES

Add a guideline to line 443 DISORDERS OF SHOULDER,POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT to apply to treatment of acromioclaviuclar joint sprains.

### GUIDELINE NOTE XXX MANAGEMENT OF ACROMIOCLAVICULAR JOINT SPRAIN

*Line 443, 638*

Sprain of acromioclavicular joint (ICD-10 S43.50-S43.52, and S43.60-S43.62) are only included on line 443 for Grade 4-6 sprains. Surgical management of these injuries is covered only after a trial of conservative therapy. Grade 1-3 acromioclavicular joint sprains are included only on line 638.

# Overview of Recommendations for Converting Lines to ICD-10-CM

## RENAME LINES

The current lines for joint injuries use Grade II and III to differentiate the upper line from the uncovered lower line for mild injuries. The Sports Medicine experts, as well as the Orthopedic experts, feel that these grading systems apply to only one type of injury on these lines (acromioclavicular joint sprain). They have recommended a name change for these lines to better represent the HERC intent to have more severe injuries only included on the upper, covered, lines.

Rename line 455 INTERNAL DERANGEMENT OF KNEE AND  
LIGAMENTOUS DISRUPTIONS OF THE KNEE, ~~GRADE II AND III~~  
POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT

Rename line 406: DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF  
THE ARMS AND LEGS, EXCLUDING THE KNEE, ~~GRADE II AND III~~  
POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT

## CODE PLACEMENT

No major issues

# Overview of Recommendations for Converting Lines to ICD-10-CM

## Appendix A: Recommended changes in ICD-9 format

### CREATE NEW LINES

Create new line for Achilles tendonitis, lateral epicondylitis, and medial epicondylitis. These conditions are currently on lines 516 and 531. They have evidence for effectiveness of treatment. There is good evidence for cortisone injections allowing better compliance with physical therapy and other treatment modalities, earlier mobilization, and quicker return to function.

Line XXX ACHILLES TENDONITIS, LATERAL AND MEDIAL EPICONDYLITIS

Treatment: MEDICAL AND SURGICAL THERAPY

ICD-10: 726.31, 726.32, 726.71

CPT: from 516 and 531

scoring:

Category: 7

IHLY: 2

IPS: 2

Pop: 0

Vuln: 0

Tertiary: 0

Effect: 4

Cost: 4

Need for treatment: 0.9

Score: 288 Approx line: 475

### GUIDELINES

Add a guideline to line 443 DISORDERS OF SHOULDER, POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT to apply to treatment of acromioclavicular joint sprains.

#### GUIDELINE NOTE XXX MANAGEMENT OF ACROMIOCLAVICULAR JOINT SPRAIN

*Line 443, 638*

Sprain of acromioclavicular joint (ICD-10 840.0) is only included on line 443 for Grade 4-6 sprains. Surgical management of these injuries is covered only after a trial of conservative therapy. Grade 1-3 acromioclavicular joint sprains are included only on line 638.

# Overview of Recommendations for Converting Lines to ICD-10-CM Oral Maxillofacial Surgery

*Specialty consultants:* Dr. Leon Assael

## **CREATE NEW LINES**

None

## **COMBINE MULTIPLE LINES**

None

## **DELETE LINES**

None

## **RESCORE LINES**

None

## **GUIDELINES**

None

## **RENAME LINES**

Change name of line 627 ~~CYSTS OF ORAL SOFT TISSUES~~ **INCONSEQUENTIAL CYSTS OF ORAL SOFT TISSUES** to reflect benign nature of cysts on this line

## **CODE PLACEMENT**

- 1) K09.0 (Developmental odontogenic cysts) and K09.1 (Developmental (nonodontogenic) cysts of oral region) which are currently on line 549 BENIGN NEOPLASM BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE need be moved to covered line--move to line 486 BRANCHIAL CLEFT CYST; THYROGLOSSAL DUCT CYST; CYST OF PHARYNX OR NASOPHARYNX. These diagnoses are benign but can be highly locally aggressive and can become malignant.
- 2) K00.0 (Anodontia) moves from line 675 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS to line 477 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES) to allow coverage for dentures which has a very large impact on health and quality of life.

# Overview of Recommendations for Converting Lines to ICD-10-CM Oral Maxillofacial Surgery

## Appendix A: Recommended changes in ICD-9 format

### CODE PLACEMENT

- 1) 526.0 (Developmental odontogenic cysts) and 526.1 (Developmental (nonodontogenic) cysts of oral region) which are currently on line 549 BENIGN NEOPLASM BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE need be moved to covered line--move to line 486 BRANCHIAL CLEFT CYST; THYROGLOSSAL DUCT CYST; CYST OF PHARYNX OR NASOPHARYNX. These diagnoses are benign but can be highly locally aggressive and can become malignant.
- 2) 520.0 (Anodontia) moves from line 675 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS to line 477 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES) to allow coverage for dentures which has a very large impact on health and quality of life.

# Overview of Recommendations for Converting Lines to ICD-10-CM Burns

*Specialty consultants: Nathan Kemalyan, MD; Nick Eshraghi, MD*

## CREATE NEW LINES

None

## COMBINE MULTIPLE LINES

None

## DELETE LINES

None

## RESCORE LINES

None

## GUIDELINES

None

## RENAME LINES

80 BURN, PARTIAL THICKNESS GREATER THAN 30% OF BODY SURFACE OR WITH VITAL SITE; FULL THICKNESS ~~WITH VITAL SITE~~, LESS THAN 10% OF BODY SURFACE

202 BURN, PARTIAL THICKNESS WITHOUT VITAL SITE **REQUIRING GRAFTING**, **UP TO** 40-30% OF BODY SURFACE

## CODE PLACEMENT

None

# Plastic Surgery ICD 10 Recommendations

*Specialty consultants: Dr. Jennifer Murphy*

## CREATE NEW LINES

### Line XXX

**Condition: ACUTE PERIPHERAL NERVE INJURY**

**Treatment: SURGICAL THERAPY**

ICD10: S74.00xA-S74.11x

CPT codes: CPT codes from line 531

Create a new line with diagnoses from lines 516 PERIPHERAL ENTHESOPATHIES  
Treatment: MEDICAL THERAPY and line 531 PERIPHERAL ENTHESOPATHIES  
Treatment: SURGICAL TREATMENT. The new line would be a surgical only line. The diagnoses on this line would stay on the current lines (516 and 531). Rationale: in the acute setting, urgent treatment can prevent lifelong complications and/or disability.

PLACED SENSORY NERVES ON LOWER LINES (535, 557) WITH THE EXCEPTION OF DIGITAL NERVES, WHICH REMAIN ON **ACUTE NERVE INJURY LINE**

S44.00xA-S44.42xA

S54.00xA-S54.22xA

S64.00xA-S64.498A

Codes S94.00xA-S94.22xA

The following guideline would apply to the new line

### **GUIDELINE NOTE XXX ACUTE PERIPHERAL NERVE INJURY**

*Line XXX*

Repair of acute peripheral nerve injuries are included on line XXX. Non-surgical medical care of these injuries are covered on line 535. Chronic nerve injuries are covered on line 557. **[Definition of acute vs chronic?]**

### Rescoring recommendations

Category 7

Impact on Healthy Life Years 4

Rationale: If you don't repair a nerve, you will have a residual defect. If upper extremity is desensate, will significantly impact functionality

Impact on Pain and Suffering 1

Population effects 0

Vulnerable 0

Tertiary Prevention 1

Effectiveness 3

Need for service 0.90

Net cost 2

Score 324

**Line 450**

**Divide Line 410 CHRONIC ULCER OF SKIN into 2 new lines**

1) **LINE XXX**

**CHRONIC OPEN WOUND, SUPERFICIAL; PRESSURE ULCER OF SKIN (STAGE 1 AND 2)**

**TREATMENT: MEDICAL THERAPY**

# Plastic Surgery ICD 10 Recommendations

ICD-10s: from line 410, with the exclusion of codes specified for stages 3 and 4  
CPT codes: 29580-29584 (wound wrapping); outpatient office visit codes

- i. Category 7
- ii. Impact on Healthy Life Years 1
- iii. Impact on Pain and Suffering 1
- iv. Population effects 0
- v. Vulnerable 1
- vi. Tertiary Prevention 2
- vii. Effectiveness 5
- viii. Need for service 1
  1. Frequent turning, nursing care, sometimes ointments and creams
- ix. Net cost 4
- x. Score 500
- xi. **Line 415**

## 2) LINE XXX

### **CHRONIC OPEN WOUND, DEEP; PRESSURE ULCER OF SKIN (STAGE 3 AND 4) TREATMENT: MEDICAL AND SURGICAL THERAPY**

ICD-10 codes: line 410, with the exclusion of codes specified for stages 1 and 2

CPT codes: from line 410

- i. Category 7
- ii. Impact on Healthy Life Years 4
- iii. Impact on Pain and Suffering 2
- iv. Population effects 0
- v. Vulnerable 4
- vi. Tertiary Prevention 3
- vii. Effectiveness 2
  1. Inadequate condition to enable surgical treatment to be effective.  
Poor wheelchair, inadequate supports.
- viii. Need for service
  1. Often require surgical intervention
- ix. Net cost 1
- x. Score 520
- xi. **Line 41**

## GUIDELINES

Hemangiomas are covered on this line (*new complicated hemangioma line*) when they are ulcerated, infected, [recurrently hemorrhaging](#) or function-threatening (e.g. eyelid hemangioma).

## RENAME LINES

315 ~~CRUSH~~ CLOSED INJURY OF DIGITS

## CODE PLACEMENT

The following codes mapped to the hyperbaric oxygen line, in ICD9 these specific codes are not mapped to hyperbaric oxygen. Both have some case reports but inconsistent results and very poor quality evidence. Plan to remove this mapping and leave only on Line 652.

L92.1 Necrobiosis lipoidica, not elsewhere classified 358,652

L94.2 Calcinosis cutis 358,652

## Lines attached to Issue: 65 ICD-10 review Plastic Surgery

Line	Condition	Treatment
216	DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	MEDICAL AND SURGICAL TREATMENT
315	CLOSED INJURIES OF DIGITS	MEDICAL AND SURGICAL TREATMENT
410	CHRONIC ULCER OF SKIN	MEDICAL AND SURGICAL TREATMENT
633	KELOID SCAR; OTHER ABNORMAL GRANULATION TISSUE	INTRALESIONAL INJECTIONS/DESTRUCTION/EXCISION, RADIATION THERAPY
652	SEBORRHEIC KERATOSIS, DYSCHROMIA, AND VASCULAR DISORDERS, SCAR CONDITIONS, AND FIBROSIS OF SKIN	MEDICAL AND SURGICAL TREATMENT
668	VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR INFLAMMATION	STRIPPING/SCLEROTHERAPY, MEDICAL THERAPY

# Neurology ICD 10 Recommendations

Specialty consultants: Ray Englander

## CREATE/MERGE/DELETE/RESCORE LINES

None

## GUIDELINES

### GUIDELINE NOTE XX

Line 268

Immune-modifying therapies for multiple sclerosis are only covered for:

- 1) Relapsing remitting multiple sclerosis

They are not covered for

- 1) Primary progressive multiple sclerosis
- 2) Secondary progressive multiple sclerosis

Rationale: Secondary progressive and primary progressive multiple sclerosis do not benefit from treatment. Lots of people are treated empirically and no one stops treating them because they are fearful that ceasing treatment may cause relapse, but there is no evidence either way. These medications are very expensive. There is clearly an indication for relapsing-remitting multiple sclerosis.

Suggestions for consideration of future evidence-based medicine guidelines or Coverage Guidances:

- 1) Management of migraine headaches
- 2) Carotid endarterectomies

## RENAME LINES

Line 441 PERIPHERAL NERVE ENTRAPMENT; [PALMAR FASCIAL FIBROMATOSIS](#)

Rationale: This line has M72.0 Palmar fascial fibromatosis [Dupuytren] is on this line which is not a peripheral nerve problem. Can interfere with hand function. The line title should include an appropriate description.

## CODE PLACEMENT

Line 268 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM – removed the ataxias (G11s), just placed these on dysfunction lines relating to posture and movement and activities of daily living (ADLs)

Code	Code Description	Other lines
G11.0	Congenital nonprogressive ataxia	78,268,318,375,407
G11.1	Early-onset cerebellar ataxia	78,268,318,375,407
G11.2	Late-onset cerebellar ataxia	78,268,318,375,407
G11.3	Cerebellar ataxia with defective DNA repair	78,268,318,375,407
G11.4	Hereditary spastic paraplegia	78,268,318,375,407
G11.8	Other hereditary ataxias	78,268,318,375,407
G11.9	Hereditary ataxia, unspecified	78,268,318,375,407

Rationale: there is no effective treatment, but may need supportive durable medical equipment.

# Otolaryngology ICD-10 Recommendations

Specialty consultants: Dr. Flint and Dr. Iuga

## CREATE NEW LINES

### 1) LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS

Guideline NOTE XX

Laryngeal paralysis is covered on this line if associated with recurrent aspiration pneumonia (unilateral or bilateral) or airway obstruction (bilateral). Hoarseness is on line 543. Laryngeal stenosis is covered on this line if it causes airway obstruction.

#### Rationale:

Most laryngeal paralysis is iatrogenic, prolonged intubation causes stenosis. Bilateral paralysis causes severe airway obstruction. Unilateral paralysis most associated with aspiration and can cause recurrent aspiration pneumonias. These are serious and need to be treated.

#### ICD 10 Codes to move on this line

J38.6 Stenosis of larynx (this line only)

J38.01 Paralysis of vocal cords and larynx, unilateral (both new line and 543)

J38.02 Paralysis of vocal cords and larynx, bilateral (both new line and 543)

**CPT codes** – based on line 543 and 31528, 31529 (laryngoscopy)

#### Scoring

Category 6

Impact on healthy life years (can be any age), 7

Impact on pain and suffering 4

Population 0

Impact on vulnerable populations (head injury patients, premature babies, those with long term intubation) – 2

Tertiary Prevention – 3, very effective at preventing aspiration pneumonia

Need for service – 2

Effectiveness – 4

Score 2560

#### **New Line 80**

Appropriate because airway obstruction in kids is line49. It is fixable and once fixed it is low cost.

## COMBINE MULTIPLE LINES

## DELETE LINES

## RESCORE LINES

### Line 217 CHOANAL ATRESIA

Treatment: REPAIR OF CHOANAL ATRESIA

# Otolaryngology ICD-10 Recommendations

Current ranking:

line	Score	Category	HL Y	Suffering	PopEffects	VulnerablePop	Tertiary Prev	Effectiveness	NeedForServices	NetCost	Text 65
217	1600	6	6	1	0	0	1	5	1	3	217

Should be higher than leukoplakia and carcinoma, because it can be life threatening. Kids are obligate nose breathers. Consider reranking this – serious issue

Impact on healthy life years, currently 6, should be changed to 8

Rationale: this occurs in newborns

Increase pain and suffering – 2 (or 3)

Rationale: they can't breathe, this is uncomfortable

Tertiary prevention 1 (or 2)

New score would be 2200, which would place it around Line 131

## Line 298 SENSORINEURAL HEARING LOSS - AGE 5 OR UNDER

Treatment: COCHLEAR IMPLANT

Current ranking:

txtLine	txtScore	cmbCategory	HL Y	Suffering	PopEffects	VulnerablePop	Tertiary Prev	Effectiveness	NeedForServices	NetCost	Text 65
298	1200	7	6	2	2	0	5	4	1	2	298

Change healthy life years to 5, not fatal

Increase suffering to a 3

New score would be 1200, no change in Line number, but prioritization makes more sense

## Line 491 SENSORINEURAL HEARING LOSS - OVER AGE OF FIVE

Treatment: COCHLEAR IMPLANT

Should be ranked higher

Healthy Life Years is currently only a 3, they strongly think should be 4. Deafness in middle aged is a big problem

Suffering should be higher than a 1, should be a 2 (older than 5)

New score: 360; New Line placement: around 444

## Line 383 HEARING LOSS - AGE 5 OR UNDER

Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS

Current ranking:

txtLine	txtScore	cmbCategory	HL Y	Suffering	PopEffects	VulnerablePop	Tertiary Prev	Effectiveness	NeedForServices	NetCost	Text 65
383	720	7	5	2	0	0	5	3	1	3	383

# Otolaryngology ICD-10 Recommendations

Suffering should be a 3 (instead of 2)  
 Effectiveness should be increased from 3 to 4  
New score: 1040, New Line placement: around Line 338

## Line 498 CHRONIC SINUSITIS

txtD line	txtRankin gMethod	txtS core	cmbCat egory	H L Y	Suffe ring	PopEf fects	Vulnera blePop	Tertiar yPrev	Effectiv eness	NeedFor Services	Net Cos t	Tex t65
498	Auto Rank	200	7	3	2	0	0	0	2	1	2	502

It does have some fatality (same as acute), would change to **category 6**  
**Need to discuss impact on healthy life years – Darren to lead discussion**  
 New Score 600  
**Line 400**

*Dr. Flint to get complication rates for untreated chronic sinusitis*

## GUIDELINES

## RENAME LINES

## CODE PLACEMENT

A number of codes were moved below the funding region

- 1) Several unspecified codes were placed on low line 686
- 2) H61.92/3 Disorder of right and left external ear
- 3) Chronic myringitis, atrophic flaccid tympanic membrane, and tympanosclerosis H73.10-H84.09 moved to line 502 only. This will help with costs.
- 4) Polyps of middle ear H74.40-93 going to 502, unspecified disorders
- 5) Acquired stenosis of ear canals (H61) moved from 430 to 502
- 6) Eczematous otitis externa (H60.54s), acute contact otitis externa (H60.53) moved to contact dermatitis and eczema lines
- 7) H60.501 unspecified noninfective otitis externa, acute actinic otitis, acute chemical otitis, acute reactive, other noninfective all go below the line

## Lines attached to Issue: 88 ICD-10 review Otolaryngology

Line	Condition	Treatment
49	CONGENITAL AIRWAY OBSTRUCTION WITH OR WITHOUT CLEFT PALATE	MEDICAL AND SURGICAL TREATMENT, ORTHODONTICS
91	DEEP OPEN WOUND OF NECK, INCLUDING LARYNX; FRACTURE OF LARYNX OR TRACHEA, OPEN	REPAIR
126	FOREIGN BODY IN PHARYNX, LARYNX, TRACHEA, BRONCHUS AND ESOPHAGUS	REMOVAL OF FOREIGN BODY
171	LEUKOPLAKIA AND CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY	INCISION/EXCISION, MEDICAL THERAPY
178	ACUTE MASTOIDITIS	MASTOIDECTOMY, MEDICAL THERAPY
217	CHOANAL ATRESIA	REPAIR OF CHOANAL ATRESIA
262	LIFE-THREATENING EPISTAXIS	SEPTOPLASTY/REPAIR/CONTROL HEMORRHAGE
298	SENSORINEURAL HEARING LOSS - AGE 5 OR UNDER	COCHLEAR IMPLANT
312	CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
347	SIALOADENITIS, ABSCESS, FISTULA OF SALIVARY GLANDS	MEDICAL AND SURGICAL TREATMENT
383	HEARING LOSS - AGE 5 OR UNDER	MEDICAL THERAPY INCLUDING HEARING AIDS
388	DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS	MEDICAL THERAPY
391	ACUTE SINUSITIS	MEDICAL AND SURGICAL TREATMENT
395	STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL	MEDICAL THERAPY, TONSILLECTOMY/ADENOIDECTOMY
405	CHOLESTEATOMA; INFECTIONS OF THE PINNA	MEDICAL AND SURGICAL TREATMENT
430	BILATERAL ANOMALIES OF EXTERNAL EAR WITH IMPAIRMENT OF HEARING	RECONSTRUCT OF EAR CANAL
442	MENIERE'S DISEASE	MEDICAL AND SURGICAL TREATMENT

Line	Condition	Treatment
450	NON-MALIGNANT OTITIS EXTERNA	MEDICAL THERAPY
456	OPEN WOUND OF EAR DRUM	TYMPANOPLASTY
470	HEARING LOSS - OVER AGE OF FIVE	MEDICAL THERAPY INCLUDING HEARING AIDS
491	SENSORINEURAL HEARING LOSS - OVER AGE OF FIVE	COCHLEAR IMPLANT
498	CHRONIC SINUSITIS	MEDICAL AND SURGICAL TREATMENT
502	CHRONIC OTITIS MEDIA	PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
504	OTOSCLEROSIS	MEDICAL AND SURGICAL TREATMENT
505	FOREIGN BODY IN EAR AND NOSE	REMOVAL OF FOREIGN BODY
527	SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS	MEDICAL AND SURGICAL TREATMENT
532	NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	MEDICAL AND SURGICAL TREATMENT
539	VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM	MEDICAL AND SURGICAL TREATMENT
543	PARALYSIS OF VOCAL CORDS OR LARYNX	INCISION/EXCISION/ENDOSCOPY
548	BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES	EXCISION, RECONSTRUCTION
574	CHRONIC DISEASE OF TONSILS AND ADENOIDS	TONSILLECTOMY AND ADENOIDECTOMY
577	HEMATOMA OF AURICLE OR PINNA AND HEMATOMA OF EXTERNAL EAR	DRAINAGE
582	OPEN WOUND OF EAR DRUM	MEDICAL THERAPY
583	SPASTIC DYSPHONIA	MEDICAL THERAPY
590	CONDUCTIVE HEARING LOSS	AUDIANT BONE CONDUCTORS
599	ACUTE NON-SUPPURATIVE LABYRINTHITIS	MEDICAL THERAPY
600	DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT	EXCISION OF CYST/RHINECTOMY/PROSTHESIS

Line	Condition	Treatment
601	STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES	INCISION AND DRAINAGE, MEDICAL THERAPY
632	CONGENITAL ANOMALIES OF THE EAR WITHOUT IMPAIRMENT OF HEARING; UNILATERAL ANOMALIES OF THE EAR	OTOPLASTY, REPAIR AND AMPUTATION
650	OPEN WOUND OF INTERNAL STRUCTURES OF MOUTH WITHOUT COMPLICATION	REPAIR SOFT TISSUES
659	CYST, HEMORRHAGE, AND INFARCTION OF THYROID	SURGICAL TREATMENT
666	BENIGN POLYPS OF VOCAL CORDS	MEDICAL THERAPY, STRIPPING
673	TMJ DISORDERS	TMJ SURGERY
680	BENIGN LESIONS OF TONGUE	EXCISION

## **Section 3**

### **New Discussion Items**

## Pulmonary Valve Repair

Question: where on the Prioritized List should acquired pulmonary valve disease be located?

Question source: HERC staff, DMAP

Issue: DMAP requested a review for pairing of 424.3 (Pulmonary valve disorders) with 75561 (Cardiac MRI). On review of this question, HERC staff identified that there is currently no pulmonary valve surgical repair line on the List. The Cardiology ICD-10 review has identified acquired pulmonary valve disease (ICD-9 424.3, ICD-10 I37.0-9) as needing to move from its current line (line 363 DISEASES OF ENDOCARDIUM), which is a medical line, to a renamed line 274, DISEASES OF MITRAL, AND TRICUSPID, AND PULMONARY VALVES, which has surgical repair codes, MRI evaluation codes, etc. This change, however, will not take effect until October 1, 2013 at the earliest. It appears that this change is needed earlier to allow for surgical repair of non-congenital pulmonary valve issues. Note: congenital pulmonary valve disorders are located on lines 77 CONGENITAL PULMONARY VALVE STENOSIS and 95 CONGENITAL PULMONARY VALVE ATRESIA.

Line 363 contains the diagnoses of all non-congenital disorders of mitral, aortic, tricuspid, and pulmonary valves (424.0-.3) as well as endocarditis. It is a medical line except for 2 surgical codes (32660 and 33496). The surgical lines with these diagnoses are 237 and 274. The two surgical codes on this line need to be removed.

The CPT codes for pulmonary valve repair (33470-33478) appear only on lines 77 CONGENITAL PULMONARY VALVE STENOSIS, 95 CONGENITAL PULMONARY VALVE ATRESIA, 192 MULTIPLE VALVULAR DISEASE, and 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT. These codes need to be paired with 424.3 on the new surgical line.

### Recommendations:

- 1) Add 424.3 (pulmonary valve disorders) to line 274
  - a. Keep on line 363 for medical treatments
- 2) Rename line 274 DISEASES OF MITRAL, AND TRICUSPID, AND PULMONARY VALVES
- 3) Add pulmonary valve repair CPT codes to line 274
  - a. 33470 Valvotomy, pulmonary valve, closed heart; transventricular
  - b. 33471 Valvotomy, pulmonary valve, closed heart; via pulmonary artery
  - c. 33472 Valvotomy, pulmonary valve, open heart; with inflow occlusion
  - d. 33474 Valvotomy, pulmonary valve, open heart; with cardiopulmonary bypass
  - e. 33475 Replacement, pulmonary valve
  - f. 33476 Right ventricular resection for infundibular stenosis, with or without commissurotomy
  - g. 33478 Outflow tract augmentation (gusset), with or without commissurotomy or infundibular resection
- 4) Remove the two current surgical CPT codes from line 363 DISEASES OF ENDOCARDIUM
  - a. This line is a medical therapy line only
  - b. 32660—no longer a valid code
  - c. 33496 (Repair of non-structural prosthetic valve dysfunction with cardiopulmonary bypass)
    - i. On the current surgical lines (237 and 274)

## Pulmonary Valve Repair

**Line: 237**

Condition: DISEASES AND DISORDERS OF AORTIC VALVE (See Guideline Notes 1,6,64,65,76)

Treatment: AORTIC VALVE REPLACEMENT, VALVULOPLASTY, MEDICAL THERAPY

ICD-9: 395,424.1,V57.1-V57.3,V57.8,V58.61

CPT: 33400-33405,33410-33413,33496,33530,33620,33621,33973,33974,35452,75557-75565,75573,92960-92998,93797,93798,96150-96154,98966-98969,99051,99060,99070,99078,99201-99366,99374,99375,99379-99444,99468-99480,99605-99607

HCPCS: G0157-G0161,G0406-G0408,G0422,G0423,G0425-G0427,S0270-S0274

**Line: 274**

Condition: DISEASES OF MITRAL AND TRICUSPID VALVES (See Guideline Notes 1,6,64,65,76)

Treatment: VALVULOPLASTY, VALVE REPLACEMENT, MEDICAL THERAPY

ICD-9: 391.1,394,396,424.0,424.2,746.89,V57.1-V57.3,V57.8,V58.61

CPT: 33420-33465,33496,33530,33620,33621,33973,33974,75557-75565,75573,92960-92998,93797,93798,96150-96154,98966-98969,99051,99060,99070,99078,99201-99366,99374,99375,99379-99444,99468-99480,99605-99607

HCPCS: G0157-G0161,G0406-G0408,G0422,G0423,G0425-G0427,S0270-S0274

**Line: 363**

Condition: DISEASES OF ENDOCARDIUM (See Guideline Notes 6,64,65,76)

Treatment: MEDICAL THERAPY

ICD-9: 424,V57.1-V57.3,V57.8

CPT: 32660,33496,92960-92998,93797,93798,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99444,99468-99480,99605-99607

HCPCS: G0157-G0161,G0406-G0408,G0422,G0423,G0425-G0427,S0270-S0274

## Nasal Endoscopy for Acute Sinusitis

Question: should nasal endoscopy be covered for treatment of acute sinusitis?

Question source: DMAP, HERC staff

Issue: DMAP has requested pairing of various nasal and sinus endoscopy procedures with acute sinusitis diagnoses. These procedures are currently covered on the chronic sinusitis line (line 498) and on the nasal polyps line (line 532). Currently, several nasal endoscopy codes are on the acute sinusitis line (line 391). Many other endoscopy codes are not included on this line. All diagnoses on the acute sinusitis line related to acute sinusitis (461.0-9).

According to Medscape, the indications for endoscopic sinus endoscopy are:

- Chronic sinusitis refractory to medical treatment
- Recurrent sinusitis
- Nasal polyposis
- Antrochoanal polyps
- Sinus mucoceles
- Excision of selected tumors
- Cerebrospinal fluid (CSF) leak closure
- Orbital decompression (eg, Graves ophthalmopathy)
- Optic nerve decompression
- Dacryocystorhinostomy (DCR)
- Choanal atresia repair
- Foreign body removal
- Epistaxis control

According to the **American Academy of Otolaryngology--Head and Neck Surgery (2007)** practice guideline:

“The clinician may obtain nasal endoscopy in diagnosing or evaluating a patient with chronic rhinosinusitis or recurrent acute rhinosinusitis. *Option based on expert opinion and a preponderance of benefit over harm.* Aggregate evidence quality: **Grade D**, expert opinion. Policy level: **option**”

Review of Medline found no current reviews examining whether nasal endoscopy should be completed for acute sinusitis. No guidance was found at NICE or SIGN.

Recommendations:

- 1) Changes shown in table on the following page
  - a. Codes to remove are shown in red with a crossed out X (X)
  - b. Do not cover nasal endoscopy for acute sinusitis
    - i. ENT experts consider this a “D” recommendation procedure
  - c. Other changes are “clean up” code clarifications

<b>CPT code</b>	<b>Code description</b>	<b>Diag</b>	<b>Line 262</b>	<b>Line 391</b>	<b>Line 498</b>	<b>Line 532</b>	<b>Line 548</b>	<b>Line 654</b>
31231	Nasal endoscopy, diagnostic, unilateral or bilateral	X						
31233	Nasal/sinus endoscopy, diagnostic with maxillary sinusoscopy	X						
31235	Nasal/sinus endoscopy, diagnostic with sphenoid sinusoscopy	X						
31237	Nasal/sinus endoscopy, surgical; with biopsy, polypectomy or debridement	✗			X	X		
31238	Nasal/sinus endoscopy, surgical; with control of nasal hemorrhage		X		X	X		✗
31239	Nasal/sinus endoscopy, surgical; with dacryocystorhinostomy				X	X		X
31240	Nasal/sinus endoscopy, surgical; with concha bullosa resection				X	X		
31254	Nasal/sinus endoscopy, surgical; with ethmoidectomy, partial (anterior)				X	X		
31255	Nasal/sinus endoscopy, surgical; with ethmoidectomy, total (anterior and posterior)				X	X		
31256	Nasal/sinus endoscopy, surgical, with maxillary antrostomy		✗		X	X		
31267	Nasal/sinus endoscopy, surgical, with maxillary antrostomy; with removal of tissue from maxillary sinus				X	X		
31276	Nasal/sinus endoscopy, surgical with frontal sinus exploration, with or without removal of tissue from frontal sinus	✗		✗	X	X	✗	
31287	Nasal/sinus endoscopy, surgical, with sphenoidotomy				X	X		
31288	Nasal/sinus endoscopy, surgical, with sphenoidotomy; with removal of tissue from the sphenoid sinus				X	X		
31295	Nasal/sinus endoscopy, surgical; with dilation of maxillary sinus ostium (eg, balloon dilation), transnasal or via canine fossa			✗	X	X		
31296	Nasal/sinus endoscopy, surgical; with dilation of frontal sinus ostium (eg, balloon dilation)			✗	X	X		
31297	Nasal/sinus endoscopy, surgical; with dilation of sphenoid sinus ostium (eg, balloon dilation)			✗	X	X		

**262** LIFE-THREATENING EPISTAXIS

**391** ACUTE SINUSITIS

**498** CHRONIC SINUSITIS

**532** NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES

**548** BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES

**654** STENOSIS OF NASOLACRIMAL DUCT (ACQUIRED)

## Guideline Summary NGC-6414

### Guideline Title

Clinical practice guideline: adult sinusitis.

### Bibliographic Source(s)

Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, Gelzer A, Hamilos D, Haydon RC 3rd, Hudgins PA, Jones S, Krouse HJ, Lee LH, Mahoney MC, Marple BF, Mitchell CJ, Nathan R, Shiffman RN, Smith TL, Witsell DL. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 2007 Sep;137(3 Suppl):S1-31. [233

references] [PubMed](#) 

### Guideline Status

This is the current release of the guideline.

A scheduled review process will occur at 5 years from publication or sooner if new compelling evidence warrants earlier consideration.

## Scope

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### Disease/Condition(s)

Rhinosinusitis, defined as symptomatic inflammation of the paranasal sinuses and nasal cavity

### Guideline Category

Diagnosis  
Evaluation  
Management  
Prevention  
Treatment

### Clinical Specialty

Allergy and Immunology  
Emergency Medicine  
Family Practice  
Infectious Diseases  
Internal Medicine  
Nursing  
Otolaryngology  
Preventive Medicine  
Pulmonary Medicine  
Radiology

### Intended Users

Allied Health Personnel  
Nurses  
Physician Assistants  
Physicians

### Guideline Objective(s)

- To improve diagnostic accuracy for adult rhinosinusitis, reduce inappropriate antibiotic use, reduce inappropriate use of radiographic imaging, and promote appropriate use of ancillary tests that include nasal endoscopy, computed tomography, and testing for allergy and immune function
- To create a guideline suitable for deriving a performance measure on rhinosinusitis and training participants in guideline methodology to facilitate future development efforts

### Target Population

Adults 18 years or older with a clinical diagnosis of uncomplicated rhinosinusitis

**Note:** *Uncomplicated rhinosinusitis* is defined as rhinosinusitis without clinically evident extension of inflammation outside the paranasal sinuses and nasal cavity at the time of diagnosis (e.g., no neurologic, ophthalmologic, or soft tissue involvement).

## Interventions and Practices Considered

### Diagnosis/Evaluation

1. Targeted history
2. Physical examination
3. Anterior rhinoscopy
4. Transillumination
5. Nasal endoscopy
6. Nasal swabs
7. Antral puncture
8. Culture of nasal cavity, middle meatus, or other site
9. Imaging procedures
10. Blood tests: complete blood count (CBC), others
11. Allergy evaluation and testing
12. Immune function testing
13. Gastroesophageal reflux
14. Pulmonary function tests
15. Mucociliary dysfunction tests

### Treatment/Management

1. Watchful waiting/observation
2. Education/information
3. Systemic antibiotics
4. Topical antibiotics
5. Oral/topical steroids
6. Systemic/topical decongestants
7. Antihistamines
8. Mucolytics
9. Leukotriene modifiers
10. Nasal saline
11. Analgesics
12. Complementary and alternative medicine
13. Postural drainage/heat
14. Biopsy (excluded from guideline)
15. Sinus surgery (excluded from guideline)

### Prevention

1. Topical steroids
2. Immunotherapy
3. Nasal lavage
4. Smoking cessation
5. Hygiene
6. Education
7. Pneumococcal vaccination
8. Influenza vaccination
9. Environmental controls

## Major Outcomes Considered

- Resolution or change of the signs and symptoms associated with rhinosinusitis
- Eradication of pathogens
- Recurrence of acute disease

- Complications or adverse events
- Cost
- Adherence to therapy
- Quality of life
- Return to work or activity
- Avoidance of surgery
- Return physician visits
- Effect on comorbid conditions (e.g., allergy, asthma, gastroesophageal reflux)

## Methodology

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### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

#### Description of Methods Used to Collect/Select the Evidence

Several literature searches were performed through November 30, 2006 by American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) staff. The initial MEDLINE search using "sinusitis OR rhinosinusitis" in any field, or "sinus\* AND infect\*" in the title or abstract, yielded 18,020 potential articles:

1. *Clinical practice guidelines* were identified by limiting the MEDLINE search to 28 articles using "guideline" as a publication type or title word. Search of the National Guideline Clearinghouse ([www.guideline.gov](http://www.guideline.gov)) identified 59 guidelines with a topic of sinusitis or rhinosinusitis. After eliminating articles that did not have rhinosinusitis as the primary focus, 12 guidelines met quality criteria of being produced under the auspices of a medical association or organization and having an explicit method for ranking evidence and linking evidence to recommendations.
2. *Systematic reviews (meta-analyses)* were identified by limiting the MEDLINE search to 226 articles using a validated filter strategy for systematic reviews. Search of the Cochrane Library identified 71 relevant titles. After eliminating articles that did not have rhinosinusitis as the primary focus, 18 systematic reviews met quality criteria of having explicit criteria for conducting the literature and selecting source articles for inclusion or exclusion.
3. *Randomized controlled trials* were identified by search of the Cochrane Controlled Trials Register, which identified 515 trials with "sinusitis" or "rhinosinusitis" as a title word.
4. *Original research studies* were identified by limiting the MEDLINE search to articles with a sinusitis (MeSH term) as a focus, published in English after 1991, not containing children age 12 years or younger and not having a publication type of case report. The resulting data set of 2039 articles yielded 348 related to diagnosis, 359 to treatment, 151 to etiology, and 24 to prognosis.

#### Number of Source Documents

- *Clinical practice guidelines*: 12
- *Systematic reviews (meta-analyses)*: 18
- *Randomized controlled trials*: 515
- *Original research studies*: 348 related to diagnosis, 359 to treatment, 151 to etiology, and 24 to prognosis

### Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Weighting According to a Rating Scheme (Scheme Given)

#### Rating Scheme for the Strength of the Evidence

##### Evidence Quality for Grades of Evidence

**Grade A:** Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the guideline's target population

**Grade B:** Randomized controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies

**Grade C:** Observational studies (case control and cohort design)

**Grade D:** Expert opinion, case reports, reasoning from first principles (bench research or animal studies)

**Grade X:** Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm

### Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

The guideline was developed using an explicit and transparent a priori protocol for creating actionable statements based on supporting evidence and the associated balance of benefit and harm. The multidisciplinary guideline development panel was chosen to represent the fields of allergy, emergency medicine, family medicine, health insurance, immunology, infectious disease, internal medicine, medical informatics, nursing, otolaryngology-head and neck surgery, and radiology.

Results of all literature searches were distributed to guideline panel members at the first meeting. The materials included an evidence table of clinical practice guidelines, an evidence table of systematic reviews, full-text electronic versions of all articles in the evidence tables, and electronic listings with abstracts (if available) of the searches for randomized trials and original research. This material was supplemented, as needed, with targeted searches to address specific needs identified in writing the guideline.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

In a series of conference calls, the working group defined the scope and objectives of the proposed guideline. During the 9 months devoted to guideline development ending in April 2007, the group met twice with interval electronic review and feedback on each guideline draft to ensure accuracy of content and consistency with standardized criteria for reporting clinical practice guidelines.

The Guidelines Review Group of the Yale Center for Medical Informatics used the Guideline Elements Module from the Conference on Guidelines Standardization (GEM-COGS), the guideline implementability appraisal and extractor software, to appraise adherence of the draft guideline to methodologic standards, to improve clarity of recommendations, and to predict potential obstacles to implementation. Panel members received summary appraisals in March 2007 and modified an advanced draft of the guideline.

## Rating Scheme for the Strength of the Recommendations

### Guideline Definitions for Evidence-Based Statements

**Strong Recommendation:** A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)\*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *Implication:* Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

**Recommendation:** A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)\*. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. *Implication:* Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.

**Option:** An option means that either the quality of evidence that exists is suspect (Grade D)\* or that well-done studies (Grade A, B, or C)\* show little clear advantage to one approach versus another. *Implication:* Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

**No Recommendation:** No recommendation means that there is both a lack of pertinent evidence (Grade D)\* and an unclear balance between benefits and harms. *Implication:* Clinicians should feel little constraint in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

\* Refer to "Rating Scheme for the Strength of the Evidence" field above for the definitions of evidence grades.

## Cost Analysis

The direct annual health-care cost of sinusitis is \$5.8 billion, which stems mainly from ambulatory and emergency department services, but also includes 500,000 surgical procedures performed on the paranasal sinuses. The indirect costs of sinusitis include 73 million days of restricted activity per year.

Acute bacterial rhinosinusitis (ABRS) has significant socioeconomic implications. The cost of initial antibiotic treatment failure in ABRS, including additional prescriptions, outpatient visits, tests, and procedures, contributes to a substantial total rhinosinusitis related health-care expenditure of more than \$3.0 billion per year in the United States. Aside from the direct treatment costs, decreased productivity and lost work days contribute to an even greater indirect health-care cost associated with this condition.

Chronic rhinosinusitis (CRS) has significant socioeconomic implications. In 2001 there were 18.3 million office visits for CRS, most of which resulted in prescription medications. Patients with CRS visit primary care clinicians twice as often as those without the disorder, and have five times as many prescriptions filled. Extrapolation of these data yields an annual direct cost for CRS of \$4.3 billion.

The following cost considerations were addressed with the recommendations:

- **Diagnosis of Acute Rhinosinusitis:** not applicable
- **Radiographic Imaging and Acute Rhinosinusitis:** savings by not performing routine radiologic imaging
- **Symptomatic Relief of Viral Rhinosinusitis (VRS):** cost of medications
- **Pain Assessment of Acute Bacterial Rhinosinusitis (ABRS):** cost of analgesic medications

- Symptomatic Relief of ABRS: cost of medications
- Watchful Waiting for ABRS: antibiotics; potential need for follow-up visit if observation failure
- Choice of Antibiotic for ABRS: cost of antibiotics
- Treatment Failure for ABRS: medication cost
- Diagnosis of Chronic Rhinosinusitis or Recurrent Acute Rhinosinusitis: none
- Modifying Factors: variable based on testing ordered
- Diagnostic Testing: relates to the specific test or procedure
- Nasal Endoscopy: procedural cost
- Radiographic Imaging: procedural cost
- Testing for Allergy and Immune Function: procedural and laboratory cost
- Prevention: minimal

## Method of Guideline Validation

External Peer Review

## Description of Method of Guideline Validation

The final draft practice guideline underwent extensive external peer review. Comments were compiled and reviewed by the group chairperson.

## Recommendations

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### Major Recommendations

The evidence grades (**A-D**) and evidence-based statements (**Strong Recommendation, Recommendation, Option, and No Recommendation**) are defined at the end of the "Major Recommendations" field.

#### 1a. Diagnosis of Acute Rhinosinusitis

Clinicians should distinguish presumed acute bacterial rhinosinusitis (ABRS) from acute rhinosinusitis caused by viral upper respiratory infections and noninfectious conditions. A clinician should diagnose ABRS when (a) symptoms or signs of acute rhinosinusitis are present 10 days or more beyond the onset of upper respiratory symptoms, or (b) symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening).

*Strong recommendation based on diagnostic studies with minor limitations and a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade B**, diagnostic studies with minor limitations regarding signs and symptoms associated with ABRS
- **Value judgments:** importance of avoiding inappropriate antibiotic treatment of viral or nonbacterial illness; emphasis on clinical signs and symptoms for initial diagnosis; importance of avoiding unnecessary diagnostic tests
- **Policy level: strong recommendation**

#### 1b. Radiographic Imaging and Acute Rhinosinusitis

Clinicians should not obtain radiographic imaging for patients who meet diagnostic criteria for acute rhinosinusitis, unless a complication or alternative diagnosis is suspected.

*Recommendation against based on diagnostic studies with minor limitations and a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade B**, diagnostic studies with minor limitations
- **Value judgments:** importance of avoiding unnecessary radiation and cost in diagnosing acute rhinosinusitis
- **Policy level: recommendation**

### 2. Symptomatic Relief of Viral Rhinosinusitis (VRS)

Clinicians may prescribe symptomatic relief in managing VRS.

*Option based on randomized trials with limitations and cohort studies with an unclear balance of benefits and harm that varies by patient.*

- **Aggregate evidence quality: Grade B and C**, randomized controlled trials with limitations and cohort studies
- **Value judgments:** provide symptomatic relief, but avoid inappropriate use of antibiotics for viral illness
- **Policy level: option**

#### 3a. Pain Assessment of Acute Bacterial Rhinosinusitis (ABRS)

The management of ABRS should include an assessment of pain. The clinician should recommend analgesic treatment based on the severity of pain.

*Strong recommendation based on randomized controlled trials of general pain relief in non-ABRS populations with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade B**, randomized controlled trials demonstrating superiority of analgesics over placebo for general pain relief, but not trials specifically regarding patients with ABRS.
- **Value judgments:** pain relief is important

- Policy level: **strong recommendation**

### 3b. Symptomatic Relief of Acute Bacterial Rhinosinusitis (ABRS)

Clinicians may prescribe symptomatic relief in managing ABRS.

*Option based on randomized trials with heterogeneous populations, diagnostic criteria, and outcome measures with a balance of benefit and harm.*

- **Aggregate evidence quality: Grade B**, randomized controlled trials with heterogeneous populations, diagnostic criteria, and outcomes measures; **Grade D**, for antihistamines (in nonatopic patients) and guaifenesin
- Value judgments: provide symptomatic relief while minimizing adverse events and costs
- Policy level: **option**

### 4. Watchful Waiting for Acute Bacterial Rhinosinusitis (ABRS)

Observation without use of antibiotics is an option for selected adults with uncomplicated ABRS who have mild illness (mild pain and temperature <38.3°C or 101°F) and assurance of follow-up.

*Option based on double-blind randomized controlled trials with heterogeneity in diagnostic criteria and illness severity, and a relative balance of benefit and risk.*

- **Aggregate evidence quality: Grade B**, randomized controlled trials with heterogeneity in diagnostic criteria and illness severity
- Value judgments: minimize drug-related adverse events and induced bacterial resistance
- Policy level: **option**

### 5. Choice of Antibiotic for Acute Bacterial Rhinosinusitis (ABRS)

If a decision is made to treat ABRS with an antibiotic agent, the clinician should prescribe amoxicillin as first-line therapy for most adults.

*Recommendation based on randomized controlled trials with heterogeneity and noninferiority design with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade B**, randomized controlled trials with heterogeneity and noninferiority design
- Value judgments: promote safe and cost-effective initial therapy
- Policy level: **recommendation**

### 6. Treatment Failure for Acute Bacterial Rhinosinusitis (ABRS)

If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.

*Recommendation based on randomized controlled trials with limitations supporting a cut point of 7 days for lack of improvement and expert opinion and first principles for changing therapy with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade B**, randomized controlled trials with limitations supporting a cut point of 7 days for lack of improvement; **Grade D**, expert opinion and first principles for changing therapy
- Value judgments: avoid excessive classification as treatment failures because of a premature time point for assessing outcomes; emphasize importance of worsening illness in definition of treatment failure
- Policy level: **recommendation**

### 7a. Diagnosis of Chronic Rhinosinusitis or Recurrent Acute Rhinosinusitis

Clinicians should distinguish chronic rhinosinusitis and recurrent acute rhinosinusitis from isolated episodes of acute bacterial rhinosinusitis and other causes of sinonasal symptoms.

*Recommendation based on cohort and observational studies with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade C**, cohort and observational studies
- Value judgments: importance of accurate diagnosis
- Policy level: **recommendation**

### 7b. Modifying Factors

Clinicians should assess the patient with chronic rhinosinusitis or recurrent acute rhinosinusitis for factors that modify management, such as allergic rhinitis, cystic fibrosis, immunocompromised state, ciliary dyskinesia, and anatomic variation.

*Recommendation based on observational studies with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade C**, observational studies
- Value judgments: consensus that identifying and managing modifying factors will improve outcomes
- Policy level: **recommendation**

### 8a. Diagnostic Testing

The clinician should corroborate a diagnosis and/or investigate for underlying causes of chronic rhinosinusitis and recurrent acute rhinosinusitis.

*Recommendation based on observational studies with a preponderance of benefit over harm.*

- **Aggregate evidence quality: Grade C**, observational studies

- Value judgments: identifying and managing underlying conditions will improve outcomes
- Policy level: **recommendation**

### 8b. Nasal Endoscopy

The clinician may obtain nasal endoscopy in diagnosing or evaluating a patient with chronic rhinosinusitis or recurrent acute rhinosinusitis.

*Option based on expert opinion and a preponderance of benefit over harm.*

- Aggregate evidence quality: **Grade D**, expert opinion
- Value judgments: importance of a detailed, complete intranasal examination
- Policy level: **option**

### 8c. Radiographic Imaging

The clinician should obtain computed tomography (CT) of the paranasal sinuses in diagnosing or evaluating a patient with chronic rhinosinusitis or recurrent acute rhinosinusitis.

*Recommendation based on diagnostic and observational studies and a preponderance of benefit over harm.*

- Aggregate evidence quality: **Grade C**, diagnostic and observational studies
- Value judgments: minimize radiation exposure and avoid unnecessary intravenous contrast
- Policy level: **recommendation**

### 8d. Testing for Allergy and Immune Function

The clinician may obtain testing for allergy and immune function in evaluating a patient with chronic rhinosinusitis or recurrent acute rhinosinusitis.

*Option based on observational studies with an unclear balance of benefit versus harm.*

- Aggregate evidence quality: **Grade C**, observational studies
- Value judgments: need to balance detecting allergy in a population with high prevalence vs. limited evidence showing benefits of allergy management on rhinosinusitis outcomes
- Policy level: **option**

## 9. Prevention

Clinicians should educate/counsel patients with chronic rhinosinusitis or recurrent acute rhinosinusitis regarding control measures.

*Recommendation based on randomized controlled trials and epidemiologic studies with limitations and a preponderance of benefit over harm.*

- Aggregate evidence quality: **Grade B**, randomized controlled trials and epidemiologic studies with limitations
- Value judgments: importance of prevention in managing patients with CRS or recurrent acute rhinosinusitis
- Policy level: **recommendation**

### Definitions:

#### Guideline Definitions for Evidence-Based Statements

**Strong Recommendation:** A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)\*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *Implication:* Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

**Recommendation:** A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)\*. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. *Implication:* Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.

**Option:** An option means that either the quality of evidence that exists is suspect (Grade D)\* or that well-done studies (Grade A, B, or C)\* show little clear advantage to one approach versus another. *Implication:* Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

**No Recommendation:** No recommendation means that there is both a lack of pertinent evidence (Grade D)\* and an unclear balance between benefits and harms. *Implication:* Clinicians should feel little constraint in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

#### Evidence Quality for Grades of Evidence

**Grade A:** Well-designed, randomized, controlled trials or diagnostic studies performed on a population similar to the guideline's target population

**Grade B:** Randomized, controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies

**Grade C:** Observational studies (case-control and cohort design)

**Grade D:** Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

**Grade X:** Exceptional situations where validating studies cannot be performed and there is a clear preponderance of

benefit over harm

### Clinical Algorithm(s)

None provided

## Evidence Supporting the Recommendations

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### Type of Evidence Supporting the Recommendations

The recommendations contained in this practice guideline were based on the best available published data through January 2007. Where data were lacking a combination of clinical experience and expert consensus was used. The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## Benefits/Harms of Implementing the Guideline Recommendations

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### Potential Benefits

- **Diagnosis of acute rhinosinusitis:** decrease inappropriate use of antibiotics for non bacterial illness; distinguish noninfectious conditions from rhinosinusitis
- **Radiographic imaging and acute rhinosinusitis:** avoid unnecessary radiation exposure; avoid delays in diagnosis from obtaining and interpreting imaging studies
- **Symptomatic relief of viral rhinosinusitis (VRS):** reduction of symptoms; avoidance of unnecessary antibiotics
- **Pain assessment of acute bacterial rhinosinusitis (ABRS):** pain reduction
- **Symptomatic relief of ABRS:** symptom relief
- **Watchful waiting for ABRS:** increase in cure or improvement at 7 to 12 days (number needed to treat [NNT] 6), and improvement at 14 to 15 days (NNT 16); reduced illness duration
- **Choice of antibiotic for ABRS:** demonstrated superiority of amoxicillin over placebo, with clinical outcomes comparable to broader-spectrum antibiotics for initial therapy; potential reduced bacterial resistance by using a narrow-spectrum antibiotic as first-line therapy; cost-effectiveness of amoxicillin versus other antibiotic choices
- **Treatment failure for ABRS:** prevent complications, detect misdiagnosis, institute effective therapy
- **Diagnosis of chronic rhinosinusitis (CRS) or recurrent acute rhinosinusitis:** distinguish conditions that might benefit from additional diagnostic evaluation and management from isolated cases of ABRS
- **Modifying factors:** identify modifying factors that would alter management of CRS or recurrent acute rhinosinusitis; identify conditions that require therapy independent of rhinosinusitis
- **Diagnostic testing:** corroborate diagnosis and identify underlying causes that may require management independent of rhinosinusitis for symptom relief
- **Nasal endoscopy:** confirm diagnosis of CRS; detect structural abnormalities, masses, lesions; perform biopsy or culture
- **Radiographic imaging:** confirm diagnosis of CRS; detect structural abnormalities, masses, lesions
- **Testing for allergy and immune function:** identify allergies or immunodeficient states that are potential modifying factors for CRS or recurrent acute rhinosinusitis
- **Prevention:** reduce symptoms and prevent exacerbations

### Potential Harms

- **Diagnosis of acute rhinosinusitis:** risk of misclassifying bacterial rhinosinusitis as viral, or vice-versa
- **Radiographic imaging and acute rhinosinusitis:** delayed diagnosis of serious underlying condition
- **Symptomatic relief of viral rhinosinusitis (VRS):** adverse effects of decongestants, antihistamines, topical steroid sprays
- **Pain assessment of acute bacterial rhinosinusitis (ABRS):** side effects of analgesic medications; potential for masking underlying illness or disease progression
- **Symptomatic relief of ABRS:** side effects of medication, which include local and systemic adverse reactions
- **Watchful waiting for ABRS:** adverse effects of specific antibiotics (number needed to harm [NNH] 9), especially gastrointestinal; societal impact of antibiotic therapy on bacterial resistance and transmission of resistant pathogens; potential disease progression in patients initially observed who do not return for follow-up
- **Choice of antibiotic for ABRS:** potential increased gastrointestinal adverse effects with amoxicillin compared to other antibiotics; adverse effects from penicillin allergy
- **Treatment failure for ABRS:** delay of up to 7 days in changing therapy if patient fails to improve
- **Diagnosis of chronic rhinosinusitis (CRS) or recurrent acute rhinosinusitis:** potential misclassification of illness because of overlapping symptomatology with other illnesses
- **Modifying factors:** identifying and treating incidental findings or subclinical conditions that might not require independent therapy; morbidity related to specific tests
- **Diagnostic testing:** related to the specific test or procedure

- Nasal endoscopy: adverse effects from topical decongestants, anesthetics, or both; discomfort; hemorrhage; trauma
- Radiographic imaging: radiation exposure
- Testing for allergy and immune function: procedural discomfort; instituting therapy based on test results with limited evidence of efficacy for CRS or recurrent acute rhinosinusitis; very rare chance of anaphylactic reactions during allergy testing
- Prevention: local irritation from saline irrigation

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## Contraindications

### Contraindications

Patients with penicillin allergy may receive a macrolide antibiotic or trimethoprim-sulfamethoxazole.

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## Qualifying Statements

### Qualifying Statements

- This clinical practice guideline is not intended as a sole source of guidance for managing adults with rhinosinusitis. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. It is not intended to replace clinical judgment or establish a protocol for all individuals with this condition, and may not provide the only appropriate approach to diagnosing and managing this problem.
- As medical knowledge expands and technology advances, clinical indicators and guidelines are promoted as conditional and provisional proposals of what is recommended under specific conditions, but they are not absolute. Guidelines are not mandates and do not and should not purport to be a legal standard of care. The responsible physician, in light of all the circumstances presented by the individual patient, must determine the appropriate treatment. Adherence to these guidelines will not ensure successful patient outcomes in every situation. The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), Inc. emphasizes that these clinical guidelines should not be deemed inclusive of all proper treatment decisions or methods of care, or exclusive of other treatment decisions or methods of care reasonably directed to obtaining the same results.

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## Implementation of the Guideline

### Description of Implementation Strategy

#### Implementation Considerations

The complete guideline is published as a supplement to *Otolaryngology–Head and Neck Surgery* to facilitate reference and distribution. The guideline will be presented to American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) members as a miniseminar at the annual meeting following publication. Existing brochures and publications by the AAO-HNSF will be updated to reflect the guideline recommendations.

An anticipated barrier to the diagnosis of rhinosinusitis is the differentiation of viral rhinosinusitis (VRS) from acute bacterial rhinosinusitis (ABRS) in a busy clinical setting. This may be assisted by a laminated teaching card or visual aid summarizing diagnostic criteria and the time course of VRS. When diagnosed with VRS, patients may pressure clinicians for antibiotics, in addition to symptomatic therapy, especially when nasal discharge is colored or purulent. Existing educational material from the Centers for Disease Control and Prevention (CDC) Get Smart Campaign can be used by clinicians to help clarify misconceptions about viral illness and nasal discharge.

Anticipated barriers to using the "observation option" for ABRS are reluctance of patients and clinicians to consider observing a presumed bacterial illness, and misinterpretation by clinicians and lay press of the statement regarding observation of ABRS as a "recommendation" instead of an "option." These barriers can be overcome with educational pamphlets and information sheets that outline the favorable natural history of nonsevere ABRS, the moderate incremental benefit of antibiotics on clinical outcomes, and the potential adverse effects of orally administered antibiotics (including induced bacterial resistance).

Some patients and clinicians might object to amoxicillin as first-line therapy for ABRS, based on assumptions that newer, more expensive alternatives "must be" more effective. Most favorable clinical outcomes for nonsevere ABRS, however, result from natural history, not antibiotics, and randomized trials of comparative efficacy do not support superiority of any single agent for initial empiric therapy. Pamphlets may help in dispelling myths about comparative efficacy.

Barriers may also be anticipated concerning guideline statements for chronic rhinosinusitis (CRS) and recurrent acute rhinosinusitis. The diagnostic criteria for these entities are unfamiliar to many clinicians, who might benefit from a summary card or teaching aid that lists these criteria along with those for ABRS and VRS. Performance of nasal endoscopy, allergy evaluation, and immunologic assessment, when appropriate, may be hindered by access to equipment and by procedural cost. Last, successfully achieving smoking cessation in patients with CRS or recurrent acute rhinosinusitis will require patient cooperation and clinician access to education materials and support services.

### Implementation Tools

#### Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## IOM Care Need

Getting Better

Living with Illness

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

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### Bibliographic Source(s)

Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, Gelzer A, Hamilos D, Haydon RC 3rd, Hudgins PA, Jones S, Krouse HJ, Lee LH, Mahoney MC, Marple BF, Mitchell CJ, Nathan R, Shiffman RN, Smith TL, Witsell DL. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 2007 Sep;137(3 Suppl):S1-31. [233

references] [PubMed](#) 

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

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### Guideline Status

This is the current release of the guideline.

A scheduled review process will occur at 5 years from publication or sooner if new compelling evidence warrants earlier consideration.

## Guideline Availability

Electronic copies: Available from the [Otolaryngology - Head and Neck Surgery Web site](#) .

Print copies: Available from Richard M. Rosenfeld, MD, MPH, Department of Otolaryngology, 339 Hicks Street, Brooklyn, NY 11201-5514; E-mail: [richrosenfeld@msn.com](mailto:richrosenfeld@msn.com)

## Availability of Companion Documents

The following is available:

- Rosenfeld RM. Executive summary. Clinical practice guideline on adult sinusitis. Otolaryngol Head Neck Surg 2007.

Electronic copies: Available to subscribers of the [Otolaryngology - Head and Neck Surgery journal](#) .

## Patient Resources

The following is available:

- **Fact sheet: Do I have sinusitis?** Electronic copies available from the [American Academy of Otolaryngology-Head and Neck Surgery \(AAO-HNS\) Web site](#) .

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## **Section 4**

### **Previously Discussed Items**

## Avascular Necrosis Of The Hip And Vascular Bone Grafting

Question: Should avascular necrosis of the hip (AVN, ICD-9 733.42) pair with vascular bone grafting (CPT 27170, bone grafting, femoral head/neck)?

Question Source: OHP managed care patient

Issue: The VbBS discussed a patient request to pair coverage of vascular bone grafting with avascular necrosis of the hip (AVN) at their February, 2012 meeting. At that meeting, evidence regarding the effectiveness of this treatment for AVN was discussed (see February packet) and expert input from Dr. Huff in orthopedics was introduced. The subcommittee requested that HERC staff work to find additional evidence for review, and find an expert willing to attend a VbBS meeting to answer questions about this procedure.

HERC staff have worked to identify an expert who performs vascular bone grafting to speak with the Commission at an upcoming meeting. Staff have contacted numerous orthopedists in Oregon, as well as at the University of Washington in Seattle, and, despite numerous attempts, no provider has been found who currently performs this type of surgery in Oregon or nearby areas. HERC staff have also attempted to contact Dr. Urbaniak, a nationally recognized expert in this procedure, at Duke, but have been unsuccessful at reaching him either via phone or email. Dr. Mararchi from OHSU has performed this surgery in the past and is available to answer questions by phone at this meeting.

Evidence:

The Center for Evidence Based Policy has completed a new independent evidence review on this topic, which is attached. The summary of this report and other relevant excerpts are included below:

There is currently little consensus among hips surgeons about the optimal treatment of avascular necrosis of the femoral head (McGrory 2007).

McGrory et al (2007) surveyed all 753 members of the American Association of Hip and Knee Surgeons (AAHKS) who devoted greater than 50% of their time to hip and knee arthroplasty. Of the 403 (54%) respondents, total hip replacement was the most frequent intervention offered for post-collapse (Steinberg stage IIIB, IVB, V and VI) AVN. Core decompression was the most commonly offered surgery for patient scenarios with symptomatic pre-collapse AVN (Steinberg stage IB, IIB). Vascularized and non-vascularized bone-grafting was offered less frequently...with fewer than 15% of surgeons offering it.

We identified 13 poor quality studies that addressed the Key Questions in this report; thus the overall quality of evidence is poor, and the results summarized in this report should be viewed in this context (most studies were identified to have high risk of bias). The results of this review suggest:

Natural history: of 664 hips in 576 patients, 394 (59%) developed symptoms and/or collapse of the femoral head, which causes destruction of the hip joint, arthritis and pain, during an average follow-up period of 88 months (range, 2 to 240 months)...Size and location of the lesion was associated with progression to collapse: fewer than 10%

## **Avascular Necrosis Of The Hip And Vascular Bone Grafting**

of small (less than 25% of the femoral head) medially located lesions progressed to collapse, 25% of medium-sized (25% to 50%) progressed, and 84% of large (greater than 50%) lesions progressed.

Conversion to total hip replacement after vascularized bone grafting varies based on Stage of AVN (extent of necrosis) and patient age.

Based on the better quality cohort studies (Kawate 2007; Zhao 2010), conversion to total hip replacement ranges from 12% (88% survival) to 56% (44% survival). Patients' Harris Hip Score, a measure of pain and hip function, improves after vascularized bone grafting compared to prior to the surgery.

Three poor quality case series were found comparing vascularized bone grafting to core decompression. Survival of the hip was found to be better in the vascularized bone grafting groups in these studies, but there were significant differences in the groups (mean age of patients, etc.) in these studies, and no conclusions could be drawn.

No studies were found comparing vascularized bone grafting to total hip arthroplasty. Factors found to be associated with poorer outcomes and higher likelihood for conversion to total hip replacement were 1) patients with Stage III – V disease; 2) older patients (mean age for most study patients was mid-30s and older patients with mean ages in the 40s had higher conversion rates); and 3) patients' whose AVN was due to alcohol, steroids, and idiopathic causes.

Based on eight studies reporting adverse outcomes, the proportion of patients having adverse outcomes following vascularized bone grafting ranges from approximately 5% to 26%.

These results have lead Stulberg (2003) to conclude that vascularized fibular grafting may be falling from favor due to its limited indication (for patients with Steinberg stage IIA or less severe AVN) and greater morbidity. Others emphasize that patients need to be carefully selected for vascularized bone grafting (Aldridge 2007; Aldridge 2008). Aldridge and Urbaniak (2007) recommend that symptomatic patients older than 50 years and patients older than 40 years with Stage IV disease or 50% or more involvement of the femoral head and limited hip motion be offered total hip replacement.

### Expert Input

Expert input was received from Dr. Hertzberg, at OHSU Orthopedics. He felt that vascular bone grafting can be indicated in limited cases for young (<50) patients, with more than a 25-30 year life expectancy, who are otherwise healthy, active patients who do not have collapse of the femoral head but who also have a large area of involvement of the femoral head. Dr. Hertzberg recommended that two surgeons review the case and recommend this procedure prior to authorizing the procedure.

## Avascular Necrosis Of The Hip And Vascular Bone Grafting

### Current Prioritized List status

27170 Bone graft, femoral head, neck, intertrochanteric or subtrochanteric area (includes obtaining bone graft) appears on 3 lines on the current Prioritized List:

Code	Line	Condition	Treatment
27170	297	DEFORMITY/CLOSED DISLOCATION OF JOINT	SURGICAL TREATMENT
27170	467	MALUNION AND NONUNION OF FRACTURE	SURGICAL TREATMENT
27170	531	PERIPHERAL ENTHESOPATHIES	SURGICAL TREATMENT

Note: no other use for CPT 27170 other than vascularized bone grafting of the hip was identified on review.

The diagnosis of AVN (733.42) appears on line line, 384, paired with various treatments including joint replacement and hip core decompression (with a guideline limiting use).

Code	Code Description	Line title
733.42	Aseptic necrosis of head and neck of femur	384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE

### **GUIDELINE NOTE 83, HIP CORE DECOMPRESSION**

#### *Line 384*

Hip Core Decompression (S2325) is covered only for early/pre-collapse (stage I or II; before X-ray changes are evident) avascular necrosis of the hip (femoral head and/or neck).

### HERC Staff Recommendations

1. Option 1 (HERC staff preferred):
  - a. Do not add coverage for vascular bone grafting for treatment of avascular necrosis of the hip to the Prioritized List
    - i. Poor evidence of effectiveness
    - ii. Consider review this issue again when a planned Cochrane systematic review on surgical treatment for advanced avascular necrosis is released
  - b. Remove coverage for vascular bone grafting for hip fractures and other indications as these have worse outcomes than for early stage avascular necrosis of the hip
    - i. Remove 27170 from lines 297, 467, and 531 and add to Excluded File
2. Option 2
  - a. If vascular bone grafting is added to line 384 for coverage for AVN, consider making the guideline change shown below:
    - i. Based on indications identified by experts and in the CEBP report
  - b. Remove 27170 from lines 297, 467, and 531
    - i. Later stage disease has worse outcomes and was identified as a relative contraindication to this procedure

## Avascular Necrosis Of The Hip And Vascular Bone Grafting

### **GUIDELINE NOTE 83, HIP CORE DECOMPRESSION AND VASCULAR BONE GRAFTING**

*Line 384*

Hip Core Decompression (HCPCS S2325) and vascular bone grafting (CPT 27170) are ~~is~~ covered only for early/pre-collapse (stage I or II; before X-ray changes are evident) avascular necrosis of the hip (femoral head and/or neck). Vascular bone grafting is only covered for symptomatic patients who are younger than 50 years of age, otherwise healthy and active with a 25-30 year life expectancy, who have a large area of involvement (but less than 50% involvement) of the femoral head without collapse of the femoral head, who do not have limited hip motion, and whose avascular necrosis is not due to steroids or alcohol.



## *Vascularized Bone Grafting For Avascular Necrosis of the Hip*

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Participant Request

March 2012

**Center for Evidence-based Policy  
Medicaid Evidence-based Decisions Project (MED)**

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## **About the Center for Evidence-based Policy and the Medicaid Evidence-based Decisions (MED) Project**

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### **Nature and Purpose of Participant Requests**

MED Participant Requests provide a brief description of evidence and/or policy in response to participant state inquiries. These inquiries are on topics that have not been prioritized for full reports through the formal topic selection process. Research for a Participant Request is based on a limited search of high-quality health care and academic journals, as well as policy core sources relevant to the topic. Participant Requests do not reflect a comprehensive search of literature, nor a formal review, critical appraisal, or synthesis of evidence.

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**Date of Request:** February 15, 2012

**State Requesting Information:** Oregon

**State Contact:** Catherine Livingston, MD, MPH

**Request:** What is the evidence regarding the effectiveness of vascular bone grafting for delaying or preventing total hip replacement in patients with avascular necrosis (osteonecrosis) of the hip?

## Background

### *Clinical Overview*

Avascular necrosis (AVN) of bone occurs when there is compromise in the microcirculation of an area of bone leading to death of the bone and bone marrow in the affected area. A variety of terms have been used to describe this condition including osteonecrosis, osteochondritis dissecans, and aseptic necrosis. In the hip (a ball and socket joint), this usually involves the femoral head (ball of the joint). A wide variety of factors have been associated with AVN of the femoral head (e.g., trauma, femoral neck fracture, corticosteroid use, alcohol use, sickle cell disease, chronic kidney disease, hemodialysis, pregnancy, organ transplantation, cigarette smoking, gout), but it may take a combination of factors, including genetic factors, to cause AVN (Lafforgue 2006). In adults, the majority of cases of AVN were reported to be associated with glucocorticoid and excessive alcohol use (Mont 1996). In other reports, up to 25% of cases were considered idiopathic (Lafforgue 2006). Although the exact incidence of AVN is not known, it is estimated that 10,000 to 20,000 new cases are diagnosed each year with the average age at diagnosis being between 30 and 40 years old (Mont 1996). Additionally, out of more than 500,000 total hip replacements done in the US each year, approximately 5% to 18% are done because of AVN of the femoral head (Vail 1997).

Few well-designed cohort studies of the natural history of AVN have been done. Single institution studies that have been published demonstrate variable results based on patient characteristics and whether or not patients had symptoms at the start of the study (Ohzono 1991; Min 2008; Mont 2010). From pathophysiological studies, it is estimated that AVN becomes detectable by imaging one to six months after exposure to a known risk factor (e.g., corticosteroids, femoral neck fracture) (Lafforgue 2006). One good quality systematic review of the literature summarizes what is known about the natural history or *prognosis of asymptomatic AVN* (Mont 2010). Mont and colleagues (2010) identified 16 prognostic studies of variable methodological quality that were published between 1991 and 2008. These studies included 576 patients (58% men) and 664 hips. Most of the included studies identified asymptomatic hips from imaging done on patients with one symptomatic hip. Of the 664 hips, 394 (59%) developed symptoms and/or collapse of the femoral head, which causes destruction of the hip joint, arthritis and pain, during an average follow-up period of 88 months (range, 2 to 240 months). In the subset of 13 studies (598 hips) that reported collapse as an outcome, 296 hips (49%) progressed to collapse over a mean of 49 months (range, 2 to 143 months). Size and location of the lesion was associated with progression to collapse: fewer than 10% of small (less

## Paraphilias

Question: Where should the new line for paraphilias be located on the Prioritized List?

Question Source: VbBS

Issue:

Line 513 GENDER IDENTIFICATION DISORDER, PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS was split at the March VbBS meeting into two new lines: “Gender Dysphoria” and “Paraphilias.” The paraphilias line was not scored at that meeting. HERC staff has worked with Dr. David Pollack, the mental health representative on the VbBS, to come up with a proposed line scoring for review.

As part of this review, two additional diagnoses (ego-dystonic sexual orientation and trans-sexualism) were found on the proposed Paraphilias line which were determined to be more appropriate for the Gender Dysphoria line. In DSM-5, these diagnoses are no longer distinguished from gender dysphoria.

The new line, as approved at the March meeting, appears below. The diagnoses on this line are summarized in the box following the line description.

Condition: PARAPHILIAS AND OTHER PSYCHOSEXUAL DISORDERS  
 Treatment: MEDICAL/PSYCHOTHERAPY  
 ICD-9: 302.0-302.5, 302.9  
 CPT: 90804-90815,90846-90857,90882,90887,96101,98966-98969,99051,99060,99201-99215,99241-99245,99366,99441-99444,99605-99607  
 HCPCS: G0176,G0177,G0425-G0427,H0004,H0023,H0032,H0034,H0035,H2010,H2011,H2014, H2027, H2032,H2033,S0270-S0274,S9484,T1016

ICD-9 codes currently proposed for the Paraphilias line

ICD-9 code	Code description
302.0	Ego-dystonic sexual orientation – proposed for Gender Dysphoria line
302.1	Zoophilia
302.2	Pedophilia
302.3	Transvestic fetishism
302.4	Exhibitionism
302.50	Trans-sexualism with unspecified sexual history – proposed for Gender Dysphoria line
302.9	Unspecified psychosexual disorder

*Current Ranking*

Line	Score	Category	HLY	Suffering	Pop Effects	VulnerablePop	Tertiary Prev	Effectiveness	NeedFor Services	NetCost
513	160	7	2	4	1	0	1	1	1	2

## Paraphilias

### HSC Staff Recommendations

- 1) Move 302.0 (Ego-dystonic sexual orientation) and 302.50 (Trans-sexualism with unspecified sexual history) to the new Gender Dysphoria Line
- 2) Rank the new Paraphilias line as shown below.

### Paraphilias

Category 7

HLY 3

Suff 3

Pop effects 3

Vuln 0

Tertiary 2

Effect 1 (depending on which condition)

Need for service .7 (very difficult to estimate because of the mix of conditions, with pedophilia being very high and some of the other conditions being lower, even though treatment is generally not very effective for any of them)

Net cost 3

Line score 154

Approx line placement 530

## Neoplasm of Uncertain and Unspecified Behavior ICD 10 Fix

### Question:

How should the ICD 10 list be corrected to adapt to the new “uncertain” and “unspecified” neoplasm guidance by Medicare?

Question Source: HERC Staff

### Issue:

Medicare has changed their guidance for codes to describe the diagnostic workup of neoplasms. It used to be Neoplasm of “uncertain” behavior was used before diagnosis was made. However, this is changed, and now “Neoplasm of unspecified behavior” is the appropriate way to do a diagnostic workup, and if one still does not know after pathology results exactly what the neoplasm is (benign or malignant, then it would be of “uncertain behavior”.

Previously, the HSC moved to add “Neoplasms of unspecified behavior” from the Excluded to the Diagnostic List to allow for biopsies and other diagnostic work up. However, the “Neoplasms of uncertain nature” are still on the Diagnostic List. These codes are more appropriate for the organ-specific cancer lines. Some are inappropriately on two lines (e.g. parathyroid cancer mapping both to thyroid cancer line and non-thyroid cancer line) and recommendations were made to adjust this.

HERC Staff Recommendation

See Table on following page

# Neoplasm of uncertain and unspecified behavior ICD

Thursday, March 08, 2012

1:02:35 PM

Line numbers in terms of the 10/13 Biennial Review/ICD10 Prioritized list. Attached to issue 272 Neoplasm of uncertain and unspecified behavior ICD 10 fix.

Line	Condition	Treatment
103	ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME	BONE MARROW TRANSPLANT

## ICD-10-CM Codes

Code	Code Description	Placement on other lines
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified	DMAP Excluded File(A),103(D),221(D)
D47.29	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue	DMAP Excluded File(A),103(D),221(D)

Line	Condition	Treatment
123	CANCER OF TESTIS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

## ICD-10-CM Codes

Code	Code Description	Placement on other lines
D40.10	Neoplasm of uncertain behavior of unspecified testis	123 CANCER OF TESTIS
D40.11	Neoplasm of uncertain behavior of right testis	123 CANCER OF TESTIS
D40.12	Neoplasm of uncertain behavior of left testis	123 CANCER OF TESTIS

Line	Condition	Treatment
124	CANCER OF EYE AND ORBIT	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES RADIATION THERAPY

## ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.7	Neoplasm of uncertain behavior of other specified sites	124 CANCER OF EYE AND ORBIT

Line	Condition	Treatment
137	BENIGN NEOPLASM OF THE BRAIN	CRANIOTOMY/CRANIECTOMY, LINEAR ACCELERATOR, MEDICAL THERAPY, WHICH INCLUDES RADIATION THERAPY

## ICD-10-CM Codes

Code	Code Description	Placement on other lines
D44.3	Neoplasm of uncertain behavior of pituitary gland	137 BENIGN NEOPLASM OF THE BRAIN
D44.4	Neoplasm of uncertain behavior of craniopharyngeal duct	137 BENIGN NEOPLASM OF THE BRAIN

Line	Condition	Treatment
165	CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D37.2	Neoplasm of uncertain behavior of small intestine	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
D37.3	Neoplasm of uncertain behavior of appendix	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
D37.4	Neoplasm of uncertain behavior of colon	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
D37.5	Neoplasm of uncertain behavior of rectum	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
D37.8	Neoplasm of uncertain behavior of other specified digestive organs	277(D)
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified	DMAP Excluded File(A),165(D),277(D)

Line	Condition	Treatment
197	CANCER OF BREAST	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY, RADIATION THERAPY AND BREAST RECONSTRUCTION

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.60	Neoplasm of uncertain behavior of unspecified breast	197 CANCER OF BREAST
D48.61	Neoplasm of uncertain behavior of right breast	197 CANCER OF BREAST
D48.62	Neoplasm of uncertain behavior of left breast	197 CANCER OF BREAST

Line	Condition	Treatment
207	CANCER OF SOFT TISSUE	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue	256(D)
D48.2	Neoplasm of uncertain behavior of peripheral nerves and autonomic nervous system	256(D)

Line	Condition	Treatment
208	CANCER OF BONES	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage	208 CANCER OF BONES

Line	Condition	Treatment
218	CANCER OF UTERUS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D39.0	Neoplasm of uncertain behavior of uterus	218(D),428(A)

Line	Condition	Treatment
220	CANCER OF THYROID	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D44.0	Neoplasm of uncertain behavior of thyroid gland	276(D)

Line	Condition	Treatment
221	NON-HODGKIN'S LYMPHOMAS	MEDICAL THERAPY, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D47.0	Histiocytic and mast cell tumors of uncertain behavior	221 NON-HODGKIN'S LYMPHOMAS
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified	DMAP Excluded File(A),103(D),221(D)
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue	DMAP Excluded File(A),103(D),221(D)

Line	Condition	Treatment
228	CANCER OF KIDNEY AND OTHER URINARY ORGANS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D41.00	Neoplasm of uncertain behavior of unspecified kidney	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.01	Neoplasm of uncertain behavior of right kidney	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.02	Neoplasm of uncertain behavior of left kidney	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.10	Neoplasm of uncertain behavior of unspecified renal pelvis	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.11	Neoplasm of uncertain behavior of right renal pelvis	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.12	Neoplasm of uncertain behavior of left renal pelvis	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.20	Neoplasm of uncertain behavior of unspecified ureter	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.21	Neoplasm of uncertain behavior of right ureter	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.22	Neoplasm of uncertain behavior of left ureter	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.3	Neoplasm of uncertain behavior of urethra	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.8	Neoplasm of uncertain behavior of other specified urinary organs	228 CANCER OF KIDNEY AND OTHER URINARY ORGANS
D41.9	Neoplasm of uncertain behavior of unspecified urinary organ	DMAP Excluded File(A),228(D)

Line	Condition	Treatment
229	CANCER OF STOMACH	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D37.1	Neoplasm of uncertain behavior of stomach	229 CANCER OF STOMACH

Line	Condition	Treatment
252	CANCER OF OVARY	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D39.10	Neoplasm of uncertain behavior of unspecified ovary	252 CANCER OF OVARY
D39.11	Neoplasm of uncertain behavior of right ovary	252 CANCER OF OVARY
D39.12	Neoplasm of uncertain behavior of left ovary	252 CANCER OF OVARY

Line	Condition	Treatment
275	CANCER OF PENIS AND OTHER MALE GENITAL ORGANS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D40.8	Neoplasm of uncertain behavior of other specified male genital organs	275 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
D40.9	Neoplasm of uncertain behavior of male genital organ, unspecified	DMAP Excluded File(A),275(D)

Line	Condition	Treatment
276	CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D44.10	Neoplasm of uncertain behavior of unspecified adrenal gland	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.11	Neoplasm of uncertain behavior of right adrenal gland	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.12	Neoplasm of uncertain behavior of left adrenal gland	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.2	Neoplasm of uncertain behavior of parathyroid gland	220(D),276(D)
D44.5	Neoplasm of uncertain behavior of pineal gland	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.6	Neoplasm of uncertain behavior of carotid body	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.7	Neoplasm of uncertain behavior of aortic body and other paraganglia	276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
D44.9	Neoplasm of uncertain behavior of unspecified endocrine gland	220(D),276(D),622(A)

Line	Condition	Treatment
277	CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D37.8	Neoplasm of uncertain behavior of other specified digestive organs	277(D),165
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified	DMAP Excluded File(A),165(D),277(D)

D48.3	Neoplasm of uncertain behavior of retroperitoneum	277 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY
D48.4	Neoplasm of uncertain behavior of peritoneum	277 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY

Line	Condition	Treatment
278	CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D38.1	Neoplasm of uncertain behavior of trachea, bronchus and lung	278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS
D38.2	Neoplasm of uncertain behavior of pleura	278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS
D38.3	Neoplasm of uncertain behavior of mediastinum	278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS
D38.4	Neoplasm of uncertain behavior of thymus	278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS

Line	Condition	Treatment
287	CANCER OF BLADDER AND URETER	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D41.4	Neoplasm of uncertain behavior of bladder	287 CANCER OF BLADDER AND URETER

Line	Condition	Treatment
292	CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.5	Neoplasm of uncertain behavior of skin	292 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA

Line	Condition	Treatment
311	CANCER OF VAGINA, VULVA	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D39.2	Neoplasm of uncertain behavior of placenta	311 CANCER OF VAGINA, VULVA
D39.8	Neoplasm of uncertain behavior of other specified female genital organs	311 CANCER OF VAGINA, VULVA
D39.9	Neoplasm of uncertain behavior of female genital organ, unspecified	311 CANCER OF VAGINA, VULVA

Line	Condition	Treatment
312	CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D37.01	Neoplasm of uncertain behavior of lip	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.02	Neoplasm of uncertain behavior of tongue	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.030	Neoplasm of uncertain behavior of the parotid salivary glands	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.031	Neoplasm of uncertain behavior of the sublingual salivary glands	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.032	Neoplasm of uncertain behavior of the submandibular salivary glands	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.039	Neoplasm of uncertain behavior of the major salivary glands, unspecified	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.04	Neoplasm of uncertain behavior of the minor salivary glands	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.05	Neoplasm of uncertain behavior of pharynx	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D38.0	Neoplasm of uncertain behavior of larynx	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D38.5	Neoplasm of uncertain behavior of other respiratory organs	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX

Line	Condition	Treatment
320	CANCER OF BRAIN AND NERVOUS SYSTEM	LINEAR ACCELERATOR, MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D42.0	Neoplasm of uncertain behavior of cerebral meninges	78(D),318(D),375(D),407(D)
D42.1	Neoplasm of uncertain behavior of spinal meninges	78(D),318(D),375(D),407(D)
D42.9	Neoplasm of uncertain behavior of meninges, unspecified	78(D),318(D),375(D),407(D)
D43.0	Neoplasm of uncertain behavior of brain, supratentorial	78(D),318(D),375(D),407(D)
D43.1	Neoplasm of uncertain behavior of brain, infratentorial	78(D),318(D),375(D),407(D)
D43.2	Neoplasm of uncertain behavior of brain, unspecified	78(D),318(D),375(D),407(D)
D43.3	Neoplasm of uncertain behavior of cranial nerves	320 CANCER OF BRAIN AND NERVOUS SYSTEM
D43.4	Neoplasm of uncertain behavior of spinal cord	78(D),318(D),375(D),407(D)
D43.8	Neoplasm of uncertain behavior of other specified parts of central nervous system	320 CANCER OF BRAIN AND NERVOUS SYSTEM
D43.9	Neoplasm of uncertain behavior of central nervous system, unspecified	DMAP Excluded File(A),320(D)

Line	Condition	Treatment
340	CANCER OF LIVER	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts	340 CANCER OF LIVER

Line	Condition	Treatment
356	CANCER OF PROSTATE GLAND	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D40.0	Neoplasm of uncertain behavior of prostate	356 CANCER OF PROSTATE GLAND

Line	Condition	Treatment
DIAG	DIAGNOSTIC PROCEDURES FILE	DIAGNOSTIC

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D49.0	Neoplasm of unspecified behavior of digestive system	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.1	Neoplasm of unspecified behavior of respiratory system	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.2	Neoplasm of unspecified behavior of bone, soft tissue, and skin	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.3	Neoplasm of unspecified behavior of breast	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.4	Neoplasm of unspecified behavior of bladder	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.5	Neoplasm of unspecified behavior of other genitourinary organs	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.6	Neoplasm of unspecified behavior of brain	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.81	Neoplasm of unspecified behavior of retina and choroid	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)
D49.89	Neoplasm of unspecified behavior of other specified sites	DMAP Diagnostic Procedure File(A),DMAP Excluded File(D)

Line	Condition	Treatment
EXCLU	EXCLUDED FILE	NONE

ICD-10-CM Codes

Code	Code Description	Placement on other lines
D48.9	Neoplasm of uncertain behavior, unspecified	DMAP Excluded File
D49.9	Neoplasm of unspecified behavior of unspecified site	DMAP Excluded File
Z86.03	Personal history of neoplasm of uncertain behavior	DMAP Excluded File

## Cardiac MRI

Question: Should cardiac MRI be covered for evaluation of thoracic aneurysms?

Question source: HSC/HERC, DMAP

Issue: In January, 2011, the HOSC reviewed pairing of cardiac MRI (CPT 75561-5) with thoracic aneurysms. At that time, the discussion was whether an echocardiogram or CT angiogram might be a more cost-effective way to evaluate such an aneurysm. HSC staff was asked to research this further and bring back to a future meeting. This topic was never re-examined. DMAP has been receiving additional requests for coverage of cardiac MRI for thoracic aneurysms and has requested that this pairing be re-evaluated.

To date, cardiac MRI has been limited to evaluation of congenital heart disease and valvular heart disease.

### Expert input

Dr. Howard Song, OHSU Cardiology

TTE and TEE are not sufficient to evaluate any thoracic aneurysm in my practice. these studies are complimentary to cross sectional imaging in that they are excellent for evaluation of aortic valve function, which is frequently affected by large aortic root aneurysms. These studies do not however provide accurate measurements or image the entire extent of most thoracic aneurysms. In my practice, a complete evaluation of a thoracic aneurysm would include either a TTE or TEE AND cross sectional imaging--either a CT scan or MRI. MRIs are especially useful for patients with renal insufficiency or for patients who require serial exams and would have a substantial lifetime radiation exposure related to annual CT scans over time. I think HERC/HSC should cover MRIs for thoracic aneurysms, at least in instances where CT scanning is contraindicated due to contrast sensitivity, renal impairment, and radiation exposure.

Dr. Michael Shapiro, OHSU Cardiology

From my perspective, MRI is sometimes the preferred modality for many reasons:

- 1) If the aneurysm is not located at the aortic root, it will not be visualized by TTE
- 2) MRI is non-invasive and TEE is semi-invasive and requires sedation
- 3) There are sometimes other structural abnormalities associated with thoracic aneurysms that are well evaluated with MRI
- 4) MRI is the most accurate and reproducible technique for measurement of aneurysms

One reasonable way to guide resource allocation is to consider MRI for initial evaluation of the aneurysm. If the location is such that TTE can accurately assess the aneurysm and there are no other associated abnormalities that would require serial evaluation with MRI, then TTE could be used solely in follow-up

### Recommendation:

- 1) Add cardiac MRI (CPT 75561-5) to line 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE

# **Section 5**

## **Guidelines**

## ICD-10 Guideline Changes/New Guidelines Suggested for Earlier Implementation

Question: should some of the new/modified guidelines which arose through the ICD-10 process be implemented earlier than October 1, 2013 (or later)?

Question source: HERC staff, DMAP

Issue: the ICD-10 review process has modified or created new guidelines, many of which are applicable to the ICD-9 list. DMAP and HERC staff feel that some guidelines could be useful for guiding coverage at the current time, rather than waiting two or more years for implementation with the new ICD-10 List. HERC staff has identified the following guidelines as being applicable in ICD-9.

### Recommendation:

- 1) Apply the following new and modified guidelines to the October 1, 2012 Prioritized List
  - a. Note: there are two additional guidelines (urology guideline for coverage of benign neoplasms and cardiothoracic surgery changes to the VAD guideline) which are considered separately in the two attached documents

### **GUIDELINE NOTE 70, HEART-KIDNEY TRANSPLANTS**

Line 279

Patients under consideration for heart/kidney transplant must qualify for each individual type of transplant under current DMAP administrative rules and transplant center criteria with the exception of any exclusions due to heart and/or kidney disease. Qualifying renal disease is limited to Stage V or VI.

### **GUIDELINE NOTE 48, FRENULECTOMY/FRENULOTOMY**

Line 373

Frenulectomy/frenulotomy (D7960) is included on this line for the following situations:

1. ~~In the presence of ankyloglossia~~
- 2.1. When deemed to cause gingival recession
3. 2. When deemed to cause movement of the gingival margin when frenum is placed under tension.
- 4.3. Maxillary labial frenulectomy not covered until age 12 and above

### **GUIDELINE NOTE 8, BARIATRIC SURGERY**

Lines 33,607

Bariatric surgery for obesity is included on Line 33 TYPE II DIABETES MELLITUS, and Line 607 OBESITY under the following criteria:

- A) Age  $\geq$  18
- A) For inclusion on Line 33: BMI  $\geq$  35 with co-morbid type II diabetes. For inclusion on Line 607: BMI  $\geq$  35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI  $\geq$  40 without a significant co-morbidity.
- B) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
- C) Participate in the following four evaluations and meet criteria as described.
  - 1) Psychosocial evaluation: (Conducted by a licensed mental health professional)

## ICD-10 Guideline Changes/New Guidelines Suggested for Earlier Implementation

- a) Evaluation to assess potential compliance with post-operative requirements.
- b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
- c) No mental or behavioral disorder that may interfere with postoperative outcomes<sup>1</sup>.
- d) Patient with previous psychiatric illness must be stable for at least 6 months.
- 2) Medical evaluation: (Conducted by OHP primary care provider)
  - a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
  - b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
  - c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
- 3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program<sup>2</sup>)
  - a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
  - b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure<sup>3</sup> and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
- 4) Dietician evaluation: (Conducted by licensed dietician)
  - a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
  - b) Counseling in dietary lifestyle changes
- D) Participate in additional evaluations:
  - 1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

<sup>1</sup> Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

<sup>2</sup> All surgical services must be provided by a program with current certification by the American College of Surgeons (ACS) or the ~~Surgical Review Corporation (SCR)~~, American Society for Metabolic and Bariatric Surgery (ASMBS) or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365; appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of

## ICD-10 Guideline Changes/New Guidelines Suggested for Earlier Implementation

surgical outcomes. If the program is still pursuing ACS or ~~SRC~~ ASMBS certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

<sup>3</sup> Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

<sup>4</sup> The patient must meet criteria #1 , #2, and #3, and be referred by the OHP primary care provider as a medically appropriate candidate, to be approved for evaluation at a qualified bariatric surgery program.

## ICD-10 Urology Follow Up Issues

Question: How to best allow coverage of treatment for certain benign neoplasms of the urinary system which can have serious impact on health?

Question source: HERC staff

Issue: At the March, 2012 VBBS meeting, the recommendations from the Urology ICD-10 review group were reviewed. As part of that review, the urology experts had suggested adding a guideline to allow coverage for certain benign neoplasms of the urinary system which either because of bleeding, size, or other complication can have serious impact on health. The subcommittee was in favor of adding this guideline, but thought that 1) it should be implemented sooner than the ICD-10 Prioritized List, and 2) for ease of use, the ICD-9 codes for the benign neoplasm in question be added to the covered kidney cancer line with the guideline then acting to delineate when this diagnosis is covered (on the kidney cancer line) and when not covered (on the benign neoplasm line).

The ICD-9 codes in question were identified and vetted with the ICD-10 urology experts. Angiomyolipoma and concocytoma are coded under 223.0 (Benign neoplasm of kidney, except pelvis).

Recommendations:

- 1) Add 223.0 to line 228 effective October 1, 2012
  - a. Keep on line 538 BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS
- 2) Add D30.00-D30.02 to line 228 effective when ICD-10 List is implemented
  - a. Keep on line 538
- 3) Modify the following guideline which was approved to be added to lines 228 and 538 at the March 2012 meeting

### **GUIDELINE NOTE XXX TREATMENT OF BENIGN NEOPLASM OF URINARY ORGANS**

*Line 228, 538*

Treatment of benign urinary system tumors (ICD-9 223.0, ICD-10 D30.00-D30.02) is covered with evidence of bleeding or urinary obstruction. Treatment of 1) oncocytoma which is >5 cm in size or symptomatic and 2) angiomyolipoma (AML) which is >5cm in women of child bearing age or in symptomatic men or women is covered.

## VAD Guideline

**Question:** Should the VAD guideline be modified to clarify the types of VADs available for certain indications?

**Question source:** DMAP, HERC staff

**Issue:** the VAD guideline was modified at the February, 2012 VBBS meeting. DMAP has asked for clarification regarding the intent of these changes. At the February meeting, the types of VADs available for the various indications were limited to “implantable” and “temporary” VADs. These terms are confusing to DMAP and the health plans and clarification was requested. Dr. Howard Song has offered clarifying wording which is shown in the proposed guideline in the Recommendations section. The guideline as adopted in February is shown below.

### **GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES**

*Lines 108,279*

Ventricular assist devices are covered only in the following circumstances:

1. as a bridge to cardiac transplant;
2. as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; or,
3. as a bridge to recovery.

Ventricular assist devices are not covered for destination therapy.

Ventricular assist devices are covered for cardiomyopathy only when the intention is bridge to cardiac transplant.

Implantable VADs are covered for indications 1 and 2.

Temporary or short term VADs are covered for indications 1 and 3.

Additionally, HERC staff have been working to identify guidelines modified in the ICD-10 review work which should be implemented earlier than the new ICD-10 List. This guideline was identified as such a guideline eligible for earlier implementation.

#### **Recommendations:**

- 1) Accept the changes to the VAD guideline as noted below
- 2) These changes should take effect with the October 1, 2012 List

### **GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES**

*Lines 108,279*

Ventricular assist devices are covered only in the following circumstances:

1. as a bridge to cardiac transplant;
2. as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; or,
3. as a bridge to recovery.

Ventricular assist devices are not covered for destination therapy.

Ventricular assist devices are covered for cardiomyopathy only when the intention is bridge to cardiac transplant.

Long-term VADs are covered for indications 1 and 2. Long-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for greater than a month with the potential for discharge from the hospital with the device.

Temporary or short term VADs are covered for indications 1 and 3. Short-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for days or weeks with no potential for discharge from the hospital with the device.

## ESA Guideline Modification

**Question:** Should the erythropoiesis-stimulating agent guideline be modified to be consistent with new safety guidance per the package inserts?

**Question Source:** Claire Mariner, Amgen (206 902 7418)

**Issue:** Called by Claire Mariner from Amgen to let us know that due to new safety concerns, there has been a modification of their package insert, specifically with regard to chronic renal failure. This modification is a class requirement, to make the use more restrictive. Target hemoglobin is no longer recommended as a concept, as higher target hemoglobins are associated with greater harm.

Boxed warning on ESAs

**WARNING: ESAs INCREASE THE RISK OF DEATH,  
MYOCARDIAL INFARCTION, STROKE, VENOUS  
THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS  
AND TUMOR PROGRESSION OR RECURRENCE**  
*See full prescribing information for complete boxed warning.*

### HERC Staff Recommendations:

#### **GUIDELINE NOTE 7, ERYTHROPOIESIS-STIMULATING AGENT (ESA) GUIDELINE**

*Lines 33,66,79,102,103,105,123-125,131,138,144,159,165,166,168,170,181,197,198,206-208,218,220,221,228,229,231,235,243,249,252,275-278,280,287,292,310-312,314,320,339-341,352,356,366,459,622*

- A) Indicated for anemia (Hgb < 10gm/dl or Hct < 30%) induced by cancer chemotherapy given within the previous 8 weeks or in the setting of myelodysplasia.
- 1) Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, ESAs should be discontinued once the hemoglobin level reaches 10gm/dl, unless a lower hemoglobin level is sufficient to avoid the need for red blood cell (RBC) blood transfusion.
- B) Indicated for anemia (Hgb < 10gm/dl or HCT < 30%) associated with HIV/AIDS.
- 1) An endogenous erythropoietin level < 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) > 4200 mg/week.
  - 2) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, ~~ESAs should be titrated to maintain a level between 10 and 12~~ the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.
- C) Indicated for anemia (Hgb < 10 gm/dl or HCT <30%) associated with chronic renal failure, with or without dialysis.
- 1) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, ~~ESAs should be titrated to maintain a level between 11 and 12.~~ the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl. In those not on dialysis, the Hgb level should not exceed 10gm/dl.



To: Cat Livingston, MD, MPH  
From: Jeffrey Petersen  
Subject: Oregon Medicaid ESA Guidelines

Amgen  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
Direct Dial: 800-772-6436  
Fax: 866-292-6436  
www.AmgenMedInfo.com

April 3, 2012

Dear Dr. Livingston,

Amgen, Inc. (Amgen) appreciates the opportunity to review and provide comments on the draft guidelines for Erythropoiesis- Stimulating Agent (ESA) for Oregon Medicaid. Amgen believes there is a specific area where modification would provide for better alignment with Aranesp® (darbepoetin alfa) and EPOGEN® (epoetin alfa) updated prescribing information (PI) for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and patients not on dialysis.

On June 24, 2011, the US Food and Drug Administration (FDA) issued a news release regarding the modified dosing recommendations for Erythropoiesis-Stimulating Agents (ESAs) when used to treat anemia in patients with chronic kidney disease (CKD).

In this News Release, Dr. John Jenkins from the FDA stated:

“Health care practitioners should carefully consider when to begin treatment with an ESA and actively monitor dosing in patients with chronic kidney disease, keeping in mind the increased risk for serious cardiovascular events, and should talk to their patients about these potential risks. The goal is to individualize therapy and use the lowest ESA dose possible to reduce the need for red blood cell transfusions.”<sup>1</sup>

The FDA News Release further stated:

“Until now, product labels for ESAs have recommended dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 grams/deciliter (g/dL) in patients with CKD. The modified package insert removes this previous concept of a ‘target hemoglobin range.’”<sup>1</sup>

As a result, the full prescribing information for ESA products now recommends that:

“Physicians and their patients with chronic kidney disease should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions against the increased risks for serious adverse cardiovascular events. For each patient, individualize dosing and use the lowest dose of ESA sufficient to reduce the need for transfusion.”<sup>1</sup>

Oregon Medicaid DRAFT Policy	Proposed Change
Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.	<u>For all patients with CKD</u> When initiating or adjusting therapy, monitor Hb levels at least weekly until stable, then monitor at least monthly.
	For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%. For patients who do not respond adequately over a 12-week escalation period, increasing the ESA dose further is unlikely to improve response and may increase risks.
	Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusion. <sup>2,3</sup>
	<u>For patients with CKD on dialysis:</u> If the hemoglobin level approaches or exceeds 11g/dL, reduce or interrupt the ESA dose. <sup>2,3</sup>
	<u>For patients with CKD not on dialysis:</u> If the hemoglobin level exceeds 10g/dL, reduce or interrupt the ESA dose. <sup>2,3</sup>

In summary, Amgen appreciates the opportunity to provide Oregon Medicaid with these recommendations with the objective of implementing a policy aligned with the updated ESA prescribing information for patients with CKD. Amgen would be pleased to address any questions that Oregon Medicaid may have on the recommendations in this letter.

Sincerely,

  
Jeffrey Petersen, MD, FRCP  
Clinical Research Medical Director

(805) 490-5230

[jeffrey.petersen@amgen.com](mailto:jeffrey.petersen@amgen.com)

References:

1. US Food and Drug Administration. FDA News Release. June 24, 2011
2. Aranesp® (darbepoetin alfa) Prescribing Information, Amgen. 2011; v25
3. EPOGEN®(epoetin alfa) Prescribing Information, Amgen. 2011; v25

66922-R1-V1

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Aranesp safely and effectively. See full prescribing information for Aranesp.

Aranesp® (darbepoetin alfa)  
injection, for intravenous or subcutaneous use  
Initial U.S. Approval: 2001

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**  
See full prescribing information for complete boxed warning.

### Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).
- No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).

### Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Table 3, 5.3).
- Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer (5.2).
- Use the lowest dose to avoid RBC transfusions (2.3).
- Use ESAs only for anemia from myelosuppressive chemotherapy (1.2).
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.3).
- Discontinue following the completion of a chemotherapy course (2.3).

## RECENT MAJOR CHANGES

- |   |         |
|---|---------|
| • Boxed Warning   | 06/2011 |
| • Indications and Usage (1.3)   | 06/2011 |
| • Dosage and Administration: Patients with Chronic Kidney Disease (2.2)                                   | 06/2011 |
| • Warnings and Precautions: Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism (5.1) | 06/2011 |

## INDICATIONS AND USAGE

Aranesp is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to:

- Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis (1.1).
- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (1.2).

### Limitations of Use

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being (1.3).

Aranesp is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy (1.3).
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.3).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.3).

## DOSAGE AND ADMINISTRATION

- Recommended starting dose for CKD patients on dialysis (2.2):
  - 0.45 mcg/kg intravenously or subcutaneously weekly, or
  - 0.75 mcg/kg intravenously or subcutaneously every 2 weeks
- Recommended starting dose for patients with CKD not on dialysis (2.2):
  - 0.45 mcg/kg intravenously or subcutaneously at 4 week intervals
- Recommended starting dose for cancer patients on chemotherapy (2.3):
  - 2.25 mcg/kg subcutaneously weekly, or
  - 500 mcg subcutaneously every 3 weeks

## DOSAGE FORMS AND STRENGTHS

- Single-dose vials: 25, 40, 60, 100, 200, 300, and 500 mcg/1 mL, and 150 mcg/0.75 mL (3)
- Single-dose prefilled syringes: 25 mcg/0.42mL, 40 mcg/0.4mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, and 500 mcg/1 mL (3)

## CONTRAINDICATIONS

- Uncontrolled hypertension (4)
- Pure red cell aplasia (PRCA) that begins after treatment with Aranesp or other erythropoietin protein drugs (4)
- Serious allergic reactions to Aranesp (4)

## WARNINGS AND PRECAUTIONS

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using Aranesp to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit (5.1 and 14.1). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2 and 5.3).
- Hypertension: Control hypertension prior to initiating and during treatment with Aranesp (5.4).
- Seizures: Aranesp increases the risk for seizures in patients with CKD (5.5). Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.5).
- PRCA: If severe anemia and low reticulocyte count develop during Aranesp treatment, withhold Aranesp and evaluate for PRCA (5.7).

## ADVERSE REACTIONS

- Patients with CKD: Adverse reactions in ≥ 10% of Aranesp-treated patients in clinical studies were hypertension, dyspnea, peripheral edema, cough, and procedural hypotension (6.1).
- Cancer Patients Receiving Chemotherapy: Adverse reactions in ≥ 1% of Aranesp-treated patients in clinical studies were abdominal pain, edema, and thrombovascular events (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy Surveillance Program is available (8.1).
- Nursing Mothers: Exercise caution when Aranesp is administered to a nursing woman (8.3).
- Pediatric Use: Safety and efficacy not established in the initial treatment of anemic patients with CKD, in the transition from another erythropoietin in patients with CKD who are less than 1 year of age, or in pediatric patients with cancer (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2011

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

**1 INDICATIONS AND USAGE**

- 1.1 Anemia Due to Chronic Kidney Disease
- 1.2 Anemia Due to Chemotherapy in Patients With Cancer
- 1.3 Limitations of Use

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Evaluation of Iron Stores and Nutritional Factors
- 2.2 Patients with Chronic Kidney Disease
- 2.3 Patients on Cancer Chemotherapy
- 2.4 Preparation and Administration

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism
- 5.2 Prescribing and Distribution Program for Aranesp in Patients With Cancer
- 5.3 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer
- 5.4 Hypertension
- 5.5 Seizures
- 5.6 Lack or Loss of Hemoglobin Response to Aranesp
- 5.7 Pure Red Cell Aplasia
- 5.8 Serious Allergic Reactions
- 5.9 Dialysis Management
- 5.10 Laboratory Monitoring

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience
- 6.3 Immunogenicity

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
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- 8.5 Geriatric Use

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.3 Reproductive and Developmental Toxicology

**14 CLINICAL STUDIES**

- 14.1 Patients With Chronic Kidney Disease
- 14.2 Cancer Patients Receiving Chemotherapy

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### **WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

#### ***Chronic Kidney Disease:***

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions (5.1)*].

#### ***Cancer:***

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [see *Table 3, Warnings and Precautions (5.3)*].
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance [see *Warnings and Precautions (5.2)*].
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions [see *Dosage and Administration (2.3)*].
- Use ESAs only for anemia from myelosuppressive chemotherapy [see *Indications and Usage (1.2)*].
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure [see *Indications and Usage (1.3)*].
- Discontinue following the completion of a chemotherapy course [see *Dosage and Administration (2.3)*].

## 1 INDICATIONS AND USAGE

### 1.1 Anemia Due to Chronic Kidney Disease

Aranesp is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.

### 1.2 Anemia Due to Chemotherapy in Patients With Cancer

Aranesp is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

### 1.3 Limitations of Use

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.

Aranesp is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia [see *Clinical Pharmacology (12.2)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Aranesp [see *Warnings and Precautions (5.10)*].

### 2.2 Patients with Chronic Kidney Disease

**In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of Aranesp sufficient to reduce the need for RBC transfusions [see *Warnings and Precautions (5.1)*]. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events [see *Boxed Warning and Clinical Studies (14)*].**

#### For all patients with CKD

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Aranesp by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the Aranesp dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Aranesp if responsiveness does not improve.

#### For patients with CKD on dialysis:

- Initiate Aranesp treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Aranesp.
- The recommended starting dose is 0.45 mcg/kg intravenously or subcutaneously as a weekly injection or 0.75 mcg/kg once every 2 weeks as appropriate. The intravenous route is recommended for patients on hemodialysis.

#### For patients with CKD not on dialysis:

- Consider initiating Aranesp treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Aranesp, and use the lowest dose of Aranesp sufficient to reduce the need for RBC transfusions.
- The recommended starting dose is 0.45 mcg/kg body weight intravenously or subcutaneously given once at four week intervals as appropriate.

When treating patients who have chronic kidney disease and cancer, physicians should refer to *Warnings and Precautions (5.1 and 5.3)*.

Refer patients who self-administer Aranesp to the Instructions for Use [see *Patient Counseling Information (17)*].

Conversion from Epoetin alfa to Aranesp in patients with CKD on dialysis

Aranesp is administered less frequently than epoetin alfa.

- Administer Aranesp once weekly in patients who were receiving epoetin alfa 2 to 3 times weekly.
- Administer Aranesp once every 2 weeks in patients who were receiving epoetin alfa once weekly.

Estimate the starting weekly dose of Aranesp for adults and pediatric patients on the basis of the weekly epoetin alfa dose at the time of substitution (see Table 1). Maintain the route of administration (intravenous or subcutaneous injection).

**Table 1. Estimated Aranesp Starting Doses (mcg/week) for Patients With CKD on Dialysis Based on Previous Epoetin alfa Dose (Units/week)**

Previous Weekly Epoetin alfa Dose (Units/week)	Aranesp Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥ 90,000	200	200

\*For pediatric patients receiving a weekly epoetin alfa dose of < 1,500 Units/week, the available data are insufficient to determine an Aranesp conversion dose.

Conversion from Epoetin alfa to Aranesp in patients with CKD not on dialysis

The dose conversion depicted in Table 1 does not accurately estimate the once monthly dose of Aranesp.

**2.3 Patients on Cancer Chemotherapy**

Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense Aranesp [see *Warnings and Precautions (5.2)*].

Initiate Aranesp in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of Aranesp necessary to avoid RBC transfusions.

Recommended Starting Dose

The recommended starting dose and schedules are:

- 2.25 mcg/kg every week subcutaneously until completion of a chemotherapy course
- 500 mcg every 3 weeks subcutaneously until completion of a chemotherapy course

## Dose Adjustment

Dose Adjustment	Weekly Schedule	Every 3 Week Schedule
<ul style="list-style-type: none"> <li>If hemoglobin increases greater than 1 g/dL in any 2-week period or</li> <li>If hemoglobin reaches a level needed to avoid RBC transfusion</li> </ul>	Reduce dose by 40%	Reduce dose by 40%
If hemoglobin exceeds a level needed to avoid RBC transfusion	<ul style="list-style-type: none"> <li>Withhold dose until hemoglobin approaches a level where RBC transfusions may be required</li> <li>Reinitiate at a dose 40% below the previous dose</li> </ul>	<ul style="list-style-type: none"> <li>Withhold dose until hemoglobin approaches a level where RBC transfusions may be required</li> <li>Reinitiate at a dose 40% below the previous dose</li> </ul>
If hemoglobin increases by less than 1 g/dL <u>and</u> remains below 10 g/dL after 6 weeks of therapy	Increase dose to 4.5 mcg/kg/week	No dose adjustment
<ul style="list-style-type: none"> <li>If there is no response as measured by hemoglobin levels or if RBC transfusions are still required after 8 weeks of therapy</li> <li>Following completion of a chemotherapy course</li> </ul>	Discontinue Aranesp	Discontinue Aranesp

## 2.4 Preparation and Administration

- The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- Do not shake. Do not use Aranesp that has been shaken or frozen.
- Protect vials and prefilled syringes from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials or prefilled syringes exhibiting particulate matter or discoloration.
- Discard unused portion of Aranesp in vials or prefilled syringes. Do not re-enter vial.
- Do not dilute Aranesp and do not administer in conjunction with other drug solutions.

## 3 DOSAGE FORMS AND STRENGTHS

Aranesp is available as a polysorbate-containing solution.

- Single-dose vials: 25, 40, 60, 100, 200, 300, and 500 mcg Aranesp/1 mL, and 150 mcg Aranesp/0.75 mL
- Single-dose prefilled syringes: 25 mcg Aranesp/0.42 mL, 40 mcg Aranesp/0.4 mL, 60 mcg Aranesp/0.3 mL, 100 mcg Aranesp/0.5 mL, and 150 mcg Aranesp/0.3 mL, 200 mcg Aranesp/0.4 mL, 300 mcg Aranesp/0.6 mL, and 500 mcg Aranesp/1 mL

## 4 CONTRAINDICATIONS

Aranesp is contraindicated in patients with:

- Uncontrolled hypertension [see *Warnings and Precautions (5.4)*].
- Pure red cell aplasia (PRCA) that begins after treatment with Aranesp or other erythropoietin protein drugs [see *Warnings and Precautions (5.7)*].
- Serious allergic reactions to Aranesp [see *Warnings and Precautions (5.8)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), Aranesp and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using Aranesp to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit [see *Clinical Studies (14.1)*]. Use caution in patients with coexistent cardiovascular disease and stroke [see *Dosage and Administration (2.2)*]. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, Aranesp and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in Table 2.

**Table 2: Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients With CKD**

	<b>Normal Hematocrit Study (NHS) (N = 1265)</b>	<b>CHOIR (N = 1432)</b>	<b>TREAT (N = 4038)</b>
<b>Time Period of Trial</b>	1993 to 1996	2003 to 2006	2004 to 2009
<b>Population</b>	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit $30 \pm 3\%$ on epoetin alfa	CKD patients not on dialysis with hemoglobin $< 11$ g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin $\leq 11$ g/dL
<b>Hemoglobin Target; Higher vs. Lower (g/dL)</b>	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. $\geq 9.0$
<b>Median (Q1, Q3) Achieved Hemoglobin level (g/dL)</b>	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
<b>Primary Endpoint</b>	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
<b>Hazard Ratio or Relative Risk (95% CI)</b>	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
<b>Adverse Outcome for Higher Target Group</b>	All-cause mortality	All-cause mortality	Stroke
<b>Hazard Ratio or Relative Risk (95% CI)</b>	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

Normal Hematocrit Study (NHS): A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either  $14 \pm 1$  g/dL or  $10 \pm 1$  g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR = 1.27; 95% CI (1.04, 1.54);  $p=0.018$ . The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: A randomized, prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy were randomized to epoetin alfa treatment targeting a maintenance hemoglobin concentration of either 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred in 125 of the 715 patients (18%) in the higher hemoglobin group compared to 97 of the 717 patients (14%) in the lower hemoglobin group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74;  $p = 0.03$ ].

TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels  $\leq$  11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either Aranesp treatment or a matching placebo. Placebo group patients also received Aranesp when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of Aranesp treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with Aranesp treatment (see Table 2), but the risk of stroke was increased nearly two-fold in the Aranesp-treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68;  $p < 0.001$ . The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the Aranesp treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. Also, among Aranesp-treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

### Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 1 in Table 3 [*see Warnings and Precautions (5.3)*]) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75;  $p = 0.012$ ).

### Patients Having Surgery

Aranesp is not approved for reduction of RBC transfusions in patients scheduled for surgical procedures.

An increased incidence of DVT in patients receiving epoetin alfa undergoing surgical orthopedic procedures was demonstrated. In a randomized, controlled study, 680 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received epoetin alfa and standard of care (SOC) treatment ( $n = 340$ ) or SOC treatment alone ( $n = 340$ ). A higher incidence of DVTs, determined by either color flow duplex imaging or by clinical symptoms, was observed in the epoetin alfa group (16 [4.7%] patients) compared with the SOC group (7 [2.1%] patients). In addition to the 23 patients with DVTs included in the primary analysis, 19 [2.8%] patients experienced 1 other thrombovascular event (TVE) each (12 [3.5%] in the epoetin alfa group and 7 [2.1%] in the SOC group).

Increased mortality was observed in a randomized, placebo-controlled study of epoetin alfa in adult patients who were undergoing CABG surgery (7 deaths in 126 patients randomized to epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events.

## **5.2 Prescribing and Distribution Program for Aranesp in Patients With Cancer**

In order to prescribe and/or dispense Aranesp to patients with cancer and anemia due to myelosuppressive chemotherapy, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program requirements. To enroll, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance. Additionally, prior to each new course of Aranesp in patients with cancer, prescribers and patients must provide written acknowledgment of a discussion of the risks of Aranesp.

### 5.3 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 3). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Study 1) or lymphoid malignancy (Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 7 and 8).

**Table 3. Randomized, Controlled Studies With Decreased Survival and/or Decreased Locoregional Control**

Study/Tumor/(n)	Hemoglobin Target	Hemoglobin (Median; Q1, Q3*)	Primary Efficacy Outcome	Adverse Outcome for ESA-containing Arm
<b>Chemotherapy</b>				
<b>Study 1</b> Metastatic breast cancer (n = 939)	12-14 g/dL	12.9 g/dL; 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
<b>Study 2</b> Lymphoid malignancy (n = 344)	13-15 g/dL (M) 13-14 g/dL (F)	11 g/dL; 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
<b>Study 3</b> Early breast cancer (n = 733)	12.5-13 g/dL	13.1 g/dL; 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
<b>Study 4</b> Cervical cancer (n = 114)	12-14 g/dL	12.7 g/dL; 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and locoregional control
<b>Radiotherapy Alone</b>				
<b>Study 5</b> Head and neck cancer (n = 351)	≥ 15 g/dL (M) ≥ 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival
<b>Study 6</b> Head and neck cancer (n = 522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
<b>No Chemotherapy or Radiotherapy</b>				
<b>Study 7</b> Non-small cell lung cancer (n = 70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
<b>Study 8</b> Non-myeloid malignancy (n = 989)	12-13 g/dL	10.6 g/dL; 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

\*Q1= 25th percentile  
Q3= 75th percentile

#### Decreased Overall Survival

Study 1 was described in the previous section [see *Warnings and Precautions (5.1)*]. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator-assessed time to tumor progression was not

different between the 2 groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Study 2 was a randomized, double-blind study (darbepoetin alfa vs. placebo) conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Study 7 was a multicenter, randomized, double-blind study (epoetin alfa vs. placebo) in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 patients (planned accrual 300 patients), a significant difference in survival in favor of the patients in the placebo arm of the study was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Study 8 was a randomized, double-blind study (darbepoetin alfa vs. placebo) in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group than in the placebo group (8 months vs. 10.8 months; HR 1.30, 95% CI: 1.07, 1.57).

#### Decreased Progression-free Survival and Overall Survival

Study 3 was a randomized, open-label, controlled, factorial design study in which darbepoetin alfa was administered to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years. The 3-year survival rate was lower (86% vs. 90%; HR 1.42, 95% CI: 0.93, 2.18) and the 3-year relapse-free survival rate was lower (72% vs. 78%; HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Study 4 was a randomized, open-label, controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to RBC transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic adverse reactions in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%; HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%; HR 1.28, 95% CI: 0.68, 2.42).

Study 5 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins  $\geq 14$  and  $\geq 15$  g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p = 0.0008) with medians of 406 days and 745 days in the epoetin beta and placebo arms respectively. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

#### Decreased Locoregional Control

Study 6 was a randomized, open-label, controlled study conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy alone (no chemotherapy) who were randomized to receive darbepoetin alfa to maintain hemoglobin levels of 14 to 15.5 g/dL or no darbepoetin alfa. An interim analysis performed on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

## 5.4 Hypertension

Aranesp is contraindicated in patients with uncontrolled hypertension. In Aranesp clinical studies, approximately 40% of patients with CKD required initiation or intensification of antihypertensive therapy during the early phase of treatment. Hypertensive encephalopathy and seizures have been reported in patients with CKD receiving Aranesp.

Appropriately control hypertension prior to initiation of and during treatment with Aranesp. Reduce or withhold Aranesp if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions [see *Patient Counseling Information (17)*].

## 5.5 Seizures

Aranesp increases the risk of seizures in patients with CKD. During the first several months following initiation of Aranesp, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

## 5.6 Lack or Loss of Hemoglobin Response to Aranesp

For lack or loss of hemoglobin response to Aranesp, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA [see *Warnings and Precautions (5.7)*]. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to Aranesp therapy [see *Dosage and Administration (2.2)*].

## 5.7 Pure Red Cell Aplasia

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Aranesp is not approved).

If severe anemia and low reticulocyte count develop during treatment with Aranesp, withhold Aranesp and evaluate patients for neutralizing antibodies to erythropoietin. Contact Amgen (1-800-77-AMGEN) to perform assays for binding and neutralizing antibodies. Permanently discontinue Aranesp in patients who develop PRCA following treatment with Aranesp or other erythropoietin protein drugs. Do not switch patients to other ESAs.

## 5.8 Serious Allergic Reactions

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Aranesp. Immediately and permanently discontinue Aranesp and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

## 5.9 Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of Aranesp. Patients receiving Aranesp may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

## 5.10 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during Aranesp treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% [see *Dosage and Administration (2.1)*]. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin may be monitored less frequently provided hemoglobin levels remain stable.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism [see *Warnings and Precautions (5.1)*]
- Increased mortality and/or increased risk of tumor progression or recurrence in Patients With Cancer [see *Warnings and Precautions (5.3)*]
- Hypertension [see *Warnings and Precautions (5.4)*]
- Seizures [see *Warnings and Precautions (5.5)*]
- PRCA [see *Warnings and Precautions (5.7)*]
- Serious allergic reactions [see *Warnings and Precautions (5.8)*]

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

#### Patients with Chronic Kidney Disease

##### *Adult Patients*

Adverse reactions were determined based on pooled data from 5 randomized, active-controlled studies of Aranesp with a total of 1357 patients (Aranesp 766, epoetin alfa 591). The median duration of exposure for patients receiving Aranesp was 340 days, with 580 patients exposed for greater than 6 months and 360 patients exposed for greater than 1 year. The median (25th, 75th percentiles) weight-adjusted dose of Aranesp was 0.50 mcg/kg (0.32, 0.81). The median (range) age for patients administered Aranesp was 62 years (18 to 88). In the Aranesp group, 55% were male, 72% were white, 83% were receiving dialysis, and 17% were not receiving dialysis.

Table 4 lists adverse reactions occurring in  $\geq 5\%$  of patients treated with Aranesp.

**Table 4. Adverse Reactions Occurring in  $\geq 5\%$  of Patients with CKD**

<b>Adverse Reaction</b>	<b>Patients Treated With Aranesp (n = 766)</b>
Hypertension	31%
Dyspnea	17%
Peripheral edema	17%
Cough	12%
Procedural hypotension	10%
Angina pectoris	8%
Vascular access complications	8%
Fluid overload	7%
Rash/Erythema	5%
Arteriovenous graft thrombosis	5%

Rates of adverse reactions with Aranesp therapy were similar to those observed with other recombinant

erythropoietins in these studies.

#### *Pediatric Patients*

Aranesp was administered to 81 pediatric patients with CKD who had stable hemoglobin concentrations while previously receiving epoetin alfa [see *Clinical Studies (14.1)*]. In this study, the most frequently reported serious adverse reactions with Aranesp were hypertension and convulsions. The most commonly reported adverse reactions were hypertension, injection site pain, rash, and convulsions. Aranesp administration was discontinued because of injection site pain in 2 patients and moderate hypertension in a third patient.

Studies have not evaluated the effects of Aranesp when administered to pediatric patients as the initial treatment for the anemia associated with CKD.

#### Cancer Patients Receiving Chemotherapy

Adverse reactions were based on data from a randomized, double-blind, placebo-controlled study of Aranesp in 597 patients (Aranesp 301, placebo 296) with extensive stage small cell lung cancer (SCLC) receiving platinum-based chemotherapy. All patients were white, 64% were male, and the median age was 61 years (range: 28 to 82 years); 25% of the study population were from North America, Western Europe, and Australia. Patients received Aranesp at a dose of 300 mcg or placebo weekly for 4 weeks then every 3 weeks for a total of 24 weeks, and the median duration of exposure was 19 weeks (range: 1 to 26 weeks).

Adverse reactions were also based on data from 7 randomized, double-blind, placebo-controlled studies, including the SCLC study described above, that enrolled 2112 patients (Aranesp 1203, placebo 909) with non-myeloid malignancies. Most patients were white (95%), male (52%), and the median age was 63 years (range: 18 to 91 years); 73% of the study population were from North America, Western Europe, and Australia. Dosing and schedules varied by study from once weekly to once every 4 weeks, and the median duration of exposure was 12 weeks (range: 1 to 27 weeks).

**Table 5. Thrombovascular Adverse Reactions in Patients Receiving Chemotherapy**

Adverse Reaction	SCLC Study		All Placebo-controlled Studies	
	Aranesp (n = 301)	Placebo (n = 296)	Aranesp (n = 1203)	Placebo (n = 909)
Thromboembolic Adverse Reactions, n (%)	24 (8.0%)	13 (4.4%)	73 (6.1%)	37 (4.1%)
Arterial	10 (3.3%)	3 (1.0%)	15 (1.2%)	5 (0.6%)
Myocardial infarction	5 (1.7%)	0	7 (0.6%)	2 (0.2%)
Venous	14 (4.7%)	10 (3.4%)	60 (5.0%)	32 (3.5%)
Pulmonary embolism	5 (1.7%)	3 (1.0%)	16 (1.3%)	6 (0.7%)
Cerebrovascular disorders*	14 (4.7%)	9(3.0%)	20 (1.7%)	17 (1.9%)

\* "Cerebrovascular disorders" encompasses CNS hemorrhages and cerebrovascular accidents (ischemic and hemorrhagic). Events in this category may also be included under "thromboembolic adverse reactions."

In addition to the thrombovascular adverse reactions, abdominal pain and edema occurred at a higher incidence in patients taking Aranesp compared to patients on placebo. Among all placebo-controlled studies, abdominal pain (13.2% vs. 9.4%) and edema (12.8% vs. 9.7%) were reported more frequently in patients receiving Aranesp compared to the placebo group. In the SCLC study the incidence of abdominal pain (10.3% vs. 3.4%) and edema (5.6% vs. 5.1%) in the Aranesp-treated patients compared to those receiving placebo.

## 6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during postmarketing use of Aranesp:

- Seizures [see *Warnings and Precautions (5.5)*]
- PRCA [see *Warnings and Precautions (5.7)*]
- Serious allergic reactions [see *Warnings and Precautions (5.8)*]

## 6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to darbepoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) [see *Warnings and Precautions (5.7)*].

In clinical studies, the percentage of patients with antibodies to Aranesp was examined using the Biacore<sup>®</sup> assay. Sera from 1501 patients with CKD and 1159 cancer patients were tested. At baseline, prior to Aranesp treatment, binding antibodies were detected in 59 patients (4%) with CKD and 36 cancer patients (3%). During Aranesp therapy (range: 22 to 177 weeks), a follow-up sample was taken. One additional patient with CKD and 8 additional cancer patients developed antibodies capable of binding Aranesp. None of the patients had antibodies capable of neutralizing the activity of Aranesp or endogenous erythropoietin at baseline or at end of study. No clinical sequelae consistent with PRCA were associated with the presence of these antibodies.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Aranesp with the incidence of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Aranesp.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies of Aranesp use in pregnant women. In animal reproduction and developmental toxicity studies, Aranesp increased early post-implantation loss. Use Aranesp during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When Aranesp was administered intravenously to healthy pregnant rats and rabbits, there was no evidence of embryofetal toxicity or other adverse outcomes at the intravenous doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. Slightly reduced fetal weights were observed when healthy rat and rabbit mothers received doses of 1 mcg/kg or more. This dose of 1 mcg/kg is near the clinical recommended starting dose. While no adverse effects on uterine implantation occurred in animals, there was an increase in early post-implantation loss in animal fertility studies. It is not clear whether the increased post-implantation loss reflects a drug effect on the uterine environment or on the conceptus. No significant placental transfer of Aranesp was detected.

In a peri/postnatal development study, pregnant female rats received Aranesp intravenously every other day from implantation throughout pregnancy and lactation. The lowest dose tested, 0.5 mcg/kg, did not cause fetal toxicity; this dose is approximately equivalent to the clinical recommended starting dose. At maternal doses of 2.5 mcg/kg

and higher, pups had decreased fetal body weights, which correlated with a slight increase in the incidence of fetal deaths, as well as delayed eye opening and delayed preputial separation [see *Nonclinical Toxicology (13.3)*].

Women who become pregnant during Aranesp treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

### 8.3 Nursing Mothers

It is not known whether Aranesp is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp is administered to a nursing woman.

### 8.4 Pediatric Use

#### Pediatric Patients with CKD

Aranesp safety and efficacy were similar between adults and pediatric patients with CKD who were over 1 year of age when patients were transitioned from treatment with epoetin alfa to Aranesp [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1)*]. Aranesp safety and efficacy have not been established in the initial treatment of anemic pediatric patients with CKD or in the transition from another erythropoietin to Aranesp in pediatric CKD patients less than 1 year of age.

#### Pediatric Cancer Patients

The safety and efficacy of Aranesp in pediatric cancer patients have not been established.

### 8.5 Geriatric Use

Of the 1801 patients with CKD in clinical studies of Aranesp, 44% were age 65 and over, while 17% were age 75 and over. Of the 873 patients in clinical studies receiving Aranesp and concomitant cancer chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No differences in safety or efficacy were observed between older and younger patients.

## 10 OVERDOSAGE

Aranesp overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of Aranesp dosage and/or with phlebotomy, as clinically indicated [see *Pharmacodynamics (12.2)*]. Cases of severe hypertension have been observed following overdose with ESAs [see *Warnings and Precautions (5.4)*].

## 11 DESCRIPTION

Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating protein that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains. The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The approximate molecular weight of darbepoetin alfa is 37,000 daltons.

Aranesp is formulated as a sterile, colorless, preservative-free solution containing polysorbate for intravenous or subcutaneous administration. Each 1 mL contains polysorbate 80 (0.05 mg), sodium chloride (8.18 mg), sodium phosphate dibasic anhydrous (0.66 mg), and sodium phosphate monobasic monohydrate (2.12 mg) in Water for Injection, USP (pH 6.2 ± 0.2).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Aranesp stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

### 12.2 Pharmacodynamics

Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp.

### 12.3 Pharmacokinetics

#### Adult Patients with CKD

The pharmacokinetics of Aranesp were studied in patients with CKD receiving or not receiving dialysis and cancer patients receiving chemotherapy.

Following intravenous administration of Aranesp to patients with CKD receiving dialysis, Aranesp serum concentration-time profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life ( $t_{1/2}$ ) of 21 hours. The  $t_{1/2}$  of Aranesp was approximately 3-fold longer than that of epoetin alfa when administered intravenously.

Following subcutaneous administration of Aranesp to patients with CKD (receiving or not receiving dialysis), absorption was slow and  $C_{max}$  occurred at 48 hours (range: 12 to 72 hours). In patients with CKD receiving dialysis, the average  $t_{1/2}$  was 46 hours (range: 12 to 89 hours), and in patients with CKD not receiving dialysis, the average  $t_{1/2}$  was 70 hours (range: 35 to 139 hours). Aranesp apparent clearance was approximately 1.4 times faster on average in patients receiving dialysis compared to patients not receiving dialysis. The bioavailability of Aranesp in patients with CKD receiving dialysis after subcutaneous administration was 37% (range: 30% to 50%).

#### Pediatric Patients with CKD

Aranesp pharmacokinetics was studied in 12 pediatric patients (age 3 to 16 years) with CKD receiving or not receiving dialysis. Following a single intravenous or subcutaneous Aranesp dose,  $C_{max}$  and  $t_{1/2}$  were similar to those obtained in adult patients with CKD on dialysis. Following a single subcutaneous dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult patients with CKD on dialysis.

#### Adult Cancer Patients

Following the first subcutaneous dose of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) in patients with cancer, the mean  $t_{1/2}$  was 74 hours (range: 24 to 144 hours) and  $C_{max}$  was observed at 71 hours (range: 28 to 120 hours). When administered on a once every 3 week schedule, 48-hour postdose Aranesp levels after the fourth dose were similar to those after the first dose.

Over the dose range of 0.45 to 4.5 mcg/kg Aranesp administered intravenously or subcutaneously on a once weekly schedule and 4.5 to 15 mcg/kg administered subcutaneously on a once every 3 week schedule, systemic exposure was approximately proportional to dose. No evidence of accumulation was observed beyond an expected less than 2-fold increase in blood levels when compared to the initial dose.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenicity

The carcinogenic potential of Aranesp has not been evaluated in long-term animal studies. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type.

#### Mutagenicity

Aranesp was not mutagenic or clastogenic under the conditions tested. Aranesp was negative in the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell gene mutation assay (using CHO cells), and in the *in vivo* mouse erythrocyte micronucleus assay.

#### Impairment of Fertility

Aranesp increased the incidence of post-implantation losses in rats. Male and female rats received intravenous doses prior to and during mating; then females were treated 3 times weekly during the first trimester of gestation (gestation days 1, 3, 5, and 7). No effect on reproductive performance, fertility, or sperm assessment parameters were detected at any of the doses evaluated (up to 10 mcg/kg, administered 3 times weekly). The dose of 10 mcg/kg is more than 10-fold higher than the clinical recommended starting dose. An increase in post-implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg, administered 3 times weekly. The dose of 0.5 mcg/kg is approximately equivalent to the clinical recommended starting dose. Signs of exaggerated pharmacology were not observed in the mother receiving 0.5 mcg/kg or less, but were observed at 2.5 mcg/kg and higher.

### 13.3 Reproductive and Developmental Toxicology

When Aranesp was administered intravenously during organogenesis to pregnant rats (gestational days 6 to 15) and rabbits (gestational days 6 to 18), no evidence of direct embryotoxic, fetotoxic, or teratogenic outcomes were observed at the doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. The only adverse effect observed was a slight reduction in fetal weight, which occurred only at doses causing exaggerated pharmacological effects in both the rat and rabbit dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species.

No significant placental transfer of Aranesp was observed in rats; placental transfer was not evaluated in rabbits.

In a peri/postnatal development study, pregnant female rats were treated intravenously with Aranesp day 6 of gestation through day 23 of lactation at 2.5 mcg/kg and higher every other day. Pups of treated mothers had decreased fetal body weights, which correlated with slight increases in the incidences of fetal death, as well as delayed eye opening and delayed preputial separation. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no Aranesp-related effects were apparent for their offspring (F2 generation fetuses).

## 14 CLINICAL STUDIES

Clinical studies in the nephrology and chemotherapy-induced anemia clinical programs are designated with the prefixes "N" and "C", respectively.

## 14.1 Patients With Chronic Kidney Disease:

### *Patients with chronic kidney disease on dialysis: ESA effects on rates of transfusion*

In early clinical studies conducted in CKD patients on dialysis, ESAs have been shown to reduce the use of RBC transfusions. These studies enrolled patients with mean baseline hemoglobin levels of approximately 7.5 g/dL and ESAs were generally titrated to achieve a hemoglobin level of approximately 12 g/dL. Fewer transfusions were given during the ESA treatment period when compared to a pre-treatment interval.

In the Normal Hematocrit Study, the yearly transfusion rate was 51.5% in the lower hemoglobin group (10 g/dL) and 32.4% in the higher hemoglobin group (14 g/dL).

### *Patients with chronic kidney disease not on dialysis: ESA effects on rates of transfusion*

In TREAT, a randomized, double-blind trial of 4038 patients with CKD and type 2 diabetes not on dialysis, a post-hoc analysis showed that the proportion of patients receiving RBC transfusions was lower in patients administered Aranesp to target a hemoglobin of 13 g/dL compared to the control arm in which Aranesp was administered intermittently if hemoglobin concentration decreased to less than 9 g/dL (15% versus 25%, respectively). In CHOIR, a randomized open-label study of 1432 patients with CKD not on dialysis, use of an ESA to target a higher (13.5 g/dL) versus lower (11.3 g/dL) hemoglobin goal did not reduce the use of RBC transfusions. In each trial, no benefits occurred for the cardiovascular or end-stage renal disease outcomes. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile [see *Warnings and Precautions (5.1)*].

### *ESA Effects on quality of life*

Aranesp use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.

### *ESA Effects on rates of death and other serious cardiac adverse events*

Three randomized outcome trials (Normal Hematocrit Study [NHS], Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease [CHOIR], and Trial of Darbepoetin Alfa in Type 2 Diabetes and CKD [TREAT]) have been conducted in patients with CKD using Epogen/PROCRIT/Aranesp to target higher vs. lower hemoglobin levels. Though these trials were designed to establish a cardiovascular or renal benefit of targeting higher hemoglobin levels, in all 3 studies, patients randomized to the higher hemoglobin target experienced worse cardiovascular outcomes and showed no reduction in progression to ESRD. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile [see *Warnings and Precautions (5.1)*].

### *Other ESA trials*

Two studies evaluated the safety and efficacy of the de novo use of Aranesp for the correction of anemia in adult patients with CKD, and 3 studies (2 in adults and 1 in pediatric patients) assessed the ability of Aranesp to maintain hemoglobin concentrations in patients with CKD who had been receiving other recombinant erythropoietins.

## De Novo Use of Aranesp

### *Once Weekly Aranesp Starting Dose*

In 2 randomized, open-label studies, Aranesp or epoetin alfa was administered for the correction of anemia in patients with CKD who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CKD patients receiving dialysis; Study N2 evaluated patients not requiring dialysis. In both studies, the starting dose of Aranesp was 0.45 mcg/kg administered once weekly. The starting dose of epoetin alfa was 50 Units/kg 3 times weekly in Study N1 and 50 Units/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin

target range is lower than the target range of these studies [see *Dosage and Administration (2.2)*].) The primary efficacy endpoint was the proportion of patients who experienced at least a 1 g/dL increase in hemoglobin concentration to a level of at least 11 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp but not to support conclusions regarding comparisons between the 2 products.

In Study N1, the primary efficacy endpoint was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp and 84% (95% CI: 66%, 95%) of the 31 patients treated with epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp treatment was 1.1 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp and 92% (95% CI: 78%, 98%) of the 37 patients treated with epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

#### *Once Every 2 Week Aranesp Starting Dose*

In 2 single-arm studies (N3 and N4), Aranesp was administered for the correction of anemia in CKD patients not receiving dialysis. In both studies, the starting dose of Aranesp was 0.75 mcg/kg administered once every 2 weeks.

In Study N3 (study duration of 18 weeks), the hemoglobin goal (hemoglobin concentration  $\geq$  11 g/dL) was achieved by 92% (95% CI: 86%, 96%) of the 128 patients treated with Aranesp.

In Study N4 (study duration of 24 weeks), the hemoglobin goal (hemoglobin concentration of 11 to 13 g/dL) was achieved by 85% (95% CI: 77%, 93%) of the 75 patients treated with Aranesp.

#### Conversion from Other Recombinant Erythropoietins

Two studies of adults (N5 and N6) and 1 study in pediatric patients (N7) were conducted in patients who had been receiving other recombinant erythropoietins for treatment of the anemia due to CKD. The studies compared the abilities of Aranesp and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies [see *Dosage and Administration (2.2)*].) Patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp or continued with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

#### *Adult Patients*

Study N5 was a double-blind study in which 169 hemodialysis patients were randomized to treatment with Aranesp and 338 patients continued on epoetin alfa. Study N6 was an open-label study in which 347 patients were randomized to treatment with Aranesp and 175 patients were randomized to continue on epoetin alfa or epoetin beta. Of the patients randomized to Aranesp, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N5, a median weekly dose of 0.53 mcg/kg Aranesp (25th, 75th percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N6, a median weekly dose of 0.41 mcg/kg Aranesp (25th, 75th percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

#### *Pediatric Patients*

Study N7 was an open-label, randomized study conducted in the United States in pediatric patients from 1 to 18 years of age with CKD receiving or not receiving dialysis. Eighty-one patients with hemoglobin concentrations that were stable on epoetin alfa received darbepoetin alfa (subcutaneously or intravenously), and 42 patients continued to receive epoetin alfa at the current dose, schedule, and route of administration. Patients received darbepoetin alfa once weekly if previously receiving epoetin alfa 2 or 3 times weekly or once every other week if previously receiving epoetin alfa weekly. A median weekly dose of 0.41 mcg/kg darbepoetin alfa (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

## 14.2 Cancer Patients Receiving Chemotherapy

The safety and efficacy of Aranesp was assessed in two multicenter, randomized studies in patients with anemia due to the effect of concomitantly administered cancer chemotherapy. Study C1 was a randomized (1:1), placebo-controlled, double-blind, multinational study conducted in 314 patients where Aranesp was administered weekly. Study C2 was a randomized (1:1), double-blind, double-dummy, active-controlled, multinational study conducted in 705 patients where Aranesp was administered either every week or every 3 weeks. Efficacy was demonstrated by a statistically significant reduction in the proportion of patients receiving RBC transfusions among patients who were on study therapy for more than 28 days.

### *Study C1*

Study C1 was conducted in anemic patients (hemoglobin  $\leq 11$  g/dL) with non-small cell lung cancer or small cell lung cancer who were scheduled to receive at least 12 weeks of a platinum-containing chemotherapy regimen. Randomization was stratified by tumor type and region (Australia vs. Canada vs. Europe). Patients received Aranesp 2.25 mcg/kg or placebo as a weekly subcutaneous injection commencing on the first day of the chemotherapy cycle. Efficacy was determined by a reduction in the proportion of patients who received RBC transfusions between week 5 (day 29) and end of treatment period (12 weeks) in the subset of 297 randomized patients (148 Aranesp and 149 placebo) who were on-study at the beginning of study week 5. All 297 patients were white, 72% were male, 71% had non-small cell histology, and the median age was 62 years (range: 36 to 80). A significantly lower proportion of patients in the Aranesp arm received RBC transfusions during week 5 to the end of treatment compared to patients in the placebo arm (crude percentages: 26% vs. 50%;  $p < 0.001$ , based on a comparison of the difference in Kaplan-Meier proportions using the Cochran-Mantel-Haenszel strata-adjusted Chi-square test).

### *Study C2*

Study C2 was conducted in anemic patients (hemoglobin  $< 11$  g/dL) with non-myeloid malignancies receiving chemotherapy. Randomization was stratified by region (Western vs. Central/Eastern Europe), tumor type (lung and gynecological vs. others), and baseline hemoglobin ( $< 10$  vs.  $\geq 10$  g/dL); all patients received double-dummy placebo and either Aranesp 500 mcg every 3 weeks or Aranesp 2.25 mcg/kg weekly subcutaneous injections for 15 weeks. Only 1 patient was non-white, 55% were female, and the median age was 60 years (range: 20 to 86). One hundred seven patients (16%) had lung or gynecological cancer while 565 (84%) had other tumor types. In both treatment schedules, the dose was reduced by 40% of the previous dose if hemoglobin level increased by more than 1 g/dL in a 14-day period.

Efficacy was determined by a comparison of the proportion of patients who received at least 1 RBC transfusion between week 5 (day 29) and the end of treatment. Three hundred thirty-five patients in the every 3 week dosing arm and 337 patients in the weekly dosing arm remained on study through or beyond day 29 and were evaluable for efficacy. Two hundred thirty-eight patients (71%) in the every 3-week arm and 261 patients (77%) patients in the weekly arm required dose reductions. Twenty-three percent (95% CI: 18%, 28%) of patients in the every 3-week treatment schedule and 28% (95% CI: 24%, 34%) in the weekly schedule received at least 1 RBC transfusion. The observed difference in the RBC transfusion rates (every 3 week minus weekly) was -5.8% (95% CI: -12.4%, 0.8%).

### *Study C3*

#### *Lack of Efficacy in Improving Survival*

Study C3 was conducted in patients required to have a hemoglobin concentration  $\geq 9$  g/dL and  $\leq 13$  g/dL with previously untreated extensive-stage small cell lung cancer (SCLC) receiving platinum and etoposide chemotherapy. Randomization was stratified by region (Western Europe, Australia/North America, and rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2), and lactate dehydrogenase (below vs. above the upper limit of normal). Patients were randomized to receive Aranesp ( $n = 298$ ) at a dose of 300 mcg once weekly for the first 4 weeks, followed by 300 mcg once every 3 weeks for the remainder of the treatment period or placebo ( $n = 298$ ).

This study was designed to detect a prolongation in overall survival (from a median of 9 months to a median of 12 months). For the final analysis, there was no evidence of improved survival (p = 0.43, log-rank test).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Store at 36°F to 46°F (2°C to 8°C). Do not freeze.

Do not shake. Protect from light; store Aranesp in the carton until use.

Do not use Aranesp that has been shaken or frozen.

Aranesp is available in the following packages:

### Single-dose Vial

<b>1 Vial/Pack, 4 Packs/Case</b>	<b>4 Vials/Pack, 10 Packs/Case</b>
200 mcg/1 mL (NDC 55513-006-01)	25 mcg/1 mL (NDC 55513-002-04)
300 mcg/1 mL (NDC 55513-110-01)	40 mcg/1 mL (NDC 55513-003-04)
	60 mcg/1 mL (NDC 55513-004-04)
	100 mcg/1 mL (NDC 55513-005-04)
	150 mcg/0.75 mL (NDC 55513-053-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard that is manually activated to cover the needle during disposal

<b>1 Syringe/Pack, 4 Packs/Case</b>	<b>4 Syringes/Pack, 10 Packs/Case</b>
200 mcg/0.4 mL (NDC 55513-028-01)	25 mcg/0.42 mL (NDC 55513-057-04)
300 mcg/0.6 mL (NDC 55513-111-01)	40 mcg/0.4 mL (NDC 55513-021-04)
500 mcg/1 mL (NDC 55513-032-01)	60 mcg/0.3 mL (NDC 55513-023-04)
	100 mcg/0.5 mL (NDC 55513-025-04)
	150 mcg/0.3 mL (NDC 55513-027-04)

## 17 PATIENT COUNSELING INFORMATION

*See Medication Guide.*

Prior to treatment, inform patients of the risks and benefits of Aranesp.

Inform patients with cancer that they must sign the patient-healthcare provider acknowledgment form before the start of each treatment course with Aranesp and that healthcare providers must enroll and comply with the ESA APPRISE Oncology Program in order to prescribe Aranesp.

Inform patients:

- To read the Medication Guide and to review and discuss any questions or concerns with their healthcare provider before starting Aranesp and at regular intervals while receiving Aranesp.
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression [see *Warnings and Precautions (5.1, 5.3)*].
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.
- Of the need to have regular laboratory tests for hemoglobin.

Instruct patients who self-administer Aranesp of the:

- Importance of following the Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Proper disposal of used syringes, needles, and unused vials, and of the full container.

**AMGEN**<sup>®</sup>

Aranesp<sup>®</sup> (darbepoetin alfa)

**Manufactured by:**

Amgen Manufacturing Limited, a subsidiary of Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

This product, the process of its manufacture, or its use, may be covered by one or more U.S. Patents, including U.S. Patent No. 7,217,689.

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\*UltraSafe<sup>®</sup> is a registered trademark of Safety Syringes, Inc.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Epogen safely and effectively. See full prescribing information for Epogen.

Epogen® (epoetin alfa)  
injection, for intravenous or subcutaneous use  
Initial U.S. Approval: 1989

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**  
*See full prescribing information for complete boxed warning.*

### Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).

### Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Table 2, 5.3).
- Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen to patients with cancer (5.2).
- Use the lowest dose to avoid RBC transfusions (2.4).
- Use ESAs only for anemia from myelosuppressive chemotherapy (1.5).
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- Discontinue following the completion of a chemotherapy course (2.4).

### Perisurgery:

- Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended (5.1).

### RECENT MAJOR CHANGES

- |   |         |
|---|---------|
| • Boxed Warning   | 06/2011 |
| • Indications and Usage (1)   | 06/2011 |
| • Dosage and Administration: Patients with Chronic Kidney Disease (2.2)                                   | 06/2011 |
| • Warnings and Precautions: Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism (5.1) | 06/2011 |

### INDICATIONS AND USAGE

Epogen is an erythropoiesis-stimulating agent (ESA) indicated for:

- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis (1.1).
  - Zidovudine in HIV-infected patients (1.2).
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (1.3).
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery (1.4).

### Limitations of Use

Epogen has not been shown to improve quality of life, fatigue, or patient well-being (1.5).

Epogen is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy (1.5).
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- In patients scheduled for surgery who are willing to donate autologous blood (1.5).
- In patients undergoing cardiac or vascular surgery (1.5).

- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.5).

### DOSAGE AND ADMINISTRATION

- CKD Patients: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis (2.2).
- Zidovudine-treated HIV-infected Patients: 100 Units/kg 3 times weekly (2.3).
- Cancer Patients on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (children  $\geq$  5 years) (2.4).
- Surgery Patients: 300 Units/kg per day daily for 14 days or 600 Units/kg weekly (2.5).

### DOSAGE FORMS AND STRENGTHS

- Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL (3)
- Multidose vial containing benzyl alcohol: 20,000 Units/2 mL and 20,000 Units/1 mL (3)

### CONTRAINDICATIONS

- Uncontrolled hypertension (4)
- Pure red cell aplasia (PRCA) that begins after treatment with Epogen or other erythropoietin protein drugs (4)
- Serious allergic reactions to Epogen (4)
- Use of the multi-dose vials in neonates, infants, pregnant women, and nursing mothers (4)

### WARNINGS AND PRECAUTIONS

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit (5.1 and 14.1). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2 and 5.3).
- Hypertension: Control hypertension prior to initiating and during treatment with Epogen (5.4).
- Seizures: Epogen increases the risk for seizures in patients with CKD (5.5). Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.5).
- PRCA: If severe anemia and low reticulocyte count develop during Epogen treatment, withhold Epogen and evaluate for PRCA (5.7).

### ADVERSE REACTIONS

- Patients with CKD: Adverse reactions in  $\geq$  5% of Epogen-treated patients in clinical studies were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection (6.1).
- Zidovudine-treated HIV-infected Patients: Adverse reactions in  $\geq$  5% of Epogen-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation (6.1).
- Cancer Patients on Chemotherapy: Adverse reactions in  $\geq$  5% of Epogen-treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis (6.1).
- Surgery Patients: Adverse reactions in  $\geq$  5% of Epogen-treated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### USE IN SPECIFIC POPULATIONS

- Pregnancy, nursing mothers, neonates, and infants: Use single-dose vials only and do not mix with benzyl alcohol. Based on animal data, Epogen may cause fetal harm. Pregnancy Surveillance Program is available (8.1, 8.3, and 8.4).
- Pediatric Use: Safety and effectiveness have not been established in CKD patients undergoing dialysis who are less than 1 month old, pediatric patients with cancer less than 5 years old, pediatric patients with CKD not on dialysis, and pediatric patients with HIV infection (8.4).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

Revised: 06/2011

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## FULL PRESCRIBING INFORMATION

### **WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

#### *Chronic Kidney Disease:*

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions (5.1)*].

#### *Cancer:*

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [see *Table 2, Warnings and Precautions (5.3)*].
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance [see *Warnings and Precautions (5.2)*].
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions [see *Dosage and Administration (2.4)*].
- Use ESAs only for anemia from myelosuppressive chemotherapy [see *Indications and Usage (1.3)*].
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure [see *Indications and Usage (1.5)*].
- Discontinue following the completion of a chemotherapy course [see *Dosage and Administration (2.4)*].

#### *Perisurgery:*

- Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended [see *Dosage and Administration (2.5) and Warnings and Precautions (5.1)*].

## 1 INDICATIONS AND USAGE

### 1.1 Anemia Due to Chronic Kidney Disease

Epogen is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

### 1.2 Anemia Due to Zidovudine in HIV-infected Patients

Epogen is indicated for the treatment of anemia due to zidovudine administered at  $\leq 4200$  mg/week in HIV-infected patients with endogenous serum erythropoietin levels of  $\leq 500$  mUnits/mL.

### 1.3 Anemia Due to Chemotherapy in Patients With Cancer

Epogen is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

## 1.4 Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery

Epogen is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epogen is not indicated for patients who are willing to donate autologous blood preoperatively.

## 1.5 Limitations of Use

Epogen has not been shown to improve quality of life, fatigue, or patient well-being.

Epogen is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia [*see Clinical Pharmacology (12.2)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Epogen [*see Warnings and Precautions (5.11)*].

### 2.2 Patients with Chronic Kidney Disease

**In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions [*see Warnings and Precautions (5.1)*]. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events [*see Boxed Warning and Clinical Studies (14)*].**

For all patients with CKD:

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Epogen by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the Epogen dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a

hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Epogen if responsiveness does not improve.

For patients with CKD on dialysis:

- Initiate Epogen treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Epogen.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. For pediatric patients, a starting dose of 50 Units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis.

For patients with CKD not on dialysis:

- Consider initiating Epogen treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Epogen, and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

When treating patients who have chronic kidney disease and cancer, physicians should refer to *Warnings and Precautions (5.1 and 5.3)*.

Refer patients who self-administer Epogen to the Instructions for Use [*see Patient Counseling Information (17)*].

### **2.3 Zidovudine-treated HIV-infected Patients**

#### Starting Dose

The recommended starting dose in adults is 100 Units/kg as an intravenous or subcutaneous injection 3 times per week.

#### Dose Adjustment

- If hemoglobin does not increase after 8 weeks of therapy, increase Epogen dose by approximately 50 to 100 Units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 Units/kg.
- Withhold Epogen if hemoglobin exceeds 12 g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.

Discontinue Epogen if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

### **2.4 Patients on Cancer Chemotherapy**

Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense Epogen [*see Warnings and Precautions (5.2)*].

Initiate Epogen in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of Epogen necessary to avoid RBC transfusions.

### Recommended Starting Dose

Adults:

- 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40,000 Units subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 Units/kg intravenously weekly until completion of a chemotherapy course.

### Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

### Dose Increase

After the initial 4 weeks of Epogen therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week in adults or
- 60,000 Units weekly in adults
- 900 Units/kg (maximum 60,000 Units) weekly in children

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue Epogen.

## **2.5 Surgery Patients**

The recommended Epogen regimens are:

- 300 Units/kg per day subcutaneously for 14 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
- 600 Units/kg subcutaneously in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery.

Deep venous thrombosis prophylaxis is recommended during Epogen therapy [*see Warnings and Precautions (5.1)*].

## **2.6 Preparation and Administration**

- Do not shake. Do not use Epogen that has been shaken or frozen.
- Protect vials from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Discard unused portions of Epogen in preservative-free vials. Do not re-enter preservative-free vials.
- Store unused portions of Epogen in multidose vials at 36°F to 46°F (2°C to 8°C). Discard 21 days after initial entry.
- Do not dilute. Do not mix with other drug solutions except for admixing as described below:

- Preservative-free Epogen from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) in a 1:1 ratio using aseptic technique at the time of administration. Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers [see *Use in Specific Populations* (8.1, 8.3, 8.4)].

### 3 DOSAGE FORMS AND STRENGTHS

Single-dose vials: 2000, 3000, 4000, 10,000, and 40,000 Units Epogen /1 mL

Multidose vials (contains benzyl alcohol): 20,000 Units Epogen /2 mL and 20,000 Units Epogen /1 mL

### 4 CONTRAINDICATIONS

Epogen is contraindicated in patients with:

- Uncontrolled hypertension [see *Warnings and Precautions* (5.4)]
- Pure red cell aplasia (PRCA) that begins after treatment with Epogen or other erythropoietin protein drugs [see *Warnings and Precautions* (5.7)]
- Serious allergic reactions to Epogen [see *Warnings and Precautions* (5.8)]

Epogen from multidose vials contains benzyl alcohol and is contraindicated in:

- Neonates, infants, pregnant women, and nursing mothers. Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. When therapy with Epogen is needed in neonates and infants, use single-dose vials; do not admix with bacteriostatic saline containing benzyl alcohol [see *Use in Specific Populations* (8.1, 8.3, 8.4)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), Epogen and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit [see *Clinical Studies* (14.1)]. Use caution in patients with coexistent cardiovascular disease and stroke [see *Dosage and Administration* (2.2)]. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, Epogen and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in Table 1.

**Table 1: Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients With CKD**

	<b>Normal Hematocrit Study (NHS) (N = 1265)</b>	<b>CHOIR (N = 1432)</b>	<b>TREAT (N = 4038)</b>
<b>Time Period of Trial</b>	1993 to 1996	2003 to 2006	2004 to 2009
<b>Population</b>	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit $30 \pm 3\%$ on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin $\leq 11$ g/dL
<b>Hemoglobin Target; Higher vs. Lower (g/dL)</b>	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. $\geq 9.0$
<b>Median (Q1, Q3) Achieved Hemoglobin level (g/dL)</b>	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
<b>Primary Endpoint</b>	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
<b>Hazard Ratio or Relative Risk (95% CI)</b>	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
<b>Adverse Outcome for Higher Target Group</b>	All-cause mortality	All-cause mortality	Stroke
<b>Hazard Ratio or Relative Risk (95% CI)</b>	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

Normal Hematocrit Study (NHS): A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either  $14 \pm 1$  g/dL or  $10 \pm 1$  g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR=1.27; 95% CI (1.04, 1.54); p=0.018. The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: A randomized, prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy were randomized to epoetin alfa treatment targeting a maintenance hemoglobin concentration of either 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for

congestive heart failure) occurred in 125 of the 715 patients (18%) in the higher hemoglobin group compared to 97 of the 717 patients (14%) in the lower hemoglobin group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74; p = 0.03].

TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with: CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels  $\leq$  11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either darbepoetin alfa treatment or a matching placebo. Placebo group patients also received darbepoetin alfa when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of darbepoetin alfa treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with darbepoetin alfa treatment (see Table 1), but the risk of stroke was increased nearly two-fold in the darbepoetin alfa -treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68; p < 0.001. The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the darbepoetin alfa- treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. Also, among darbepoetin alfa -treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

#### Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 1 in Table 2 [*see Warnings and Precautions (5.3)*]) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

#### Patients Having Surgery

An increased incidence of deep venous thrombosis (DVT) in patients receiving epoetin alfa undergoing surgical orthopedic procedures was demonstrated [*see Adverse Reactions (6.1)*]. In a randomized, controlled study, 680 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, were randomized to 4 doses of 600 Units/kg epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment (n = 340) or to SOC treatment alone (n = 340). A higher incidence of DVTs, determined by either color flow duplex imaging or by clinical symptoms, was observed in the epoetin alfa group (16 [4.7%] patients) compared with the SOC group (7 [2.1%] patients). In addition to the 23 patients with DVTs included in the primary analysis, 19 [2.8%] patients (n = 680) experienced 1 other thrombovascular event (TVE) each (12 [3.5%] in the epoetin alfa group and 7 [2.1%] in the SOC group). Deep venous thrombosis prophylaxis is strongly recommended when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients [*see Dosage and Administration (2.5)*].

Increased mortality was observed in a randomized, placebo-controlled study of Epogen in adult patients who were undergoing CABG surgery (7 deaths in 126 patients randomized to Epogen versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events.

## 5.2 Prescribing and Distribution Program for Epogen in Patients With Cancer

In order to prescribe and/or dispense Epogen to patients with cancer and anemia due to myelosuppressive chemotherapy, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program requirements. To enroll, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance. Additionally, prior to each new course of Epogen in patients with cancer, prescribers and patients must provide written acknowledgment of a discussion of the risks of Epogen.

## 5.3 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 2). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Study 1) or lymphoid malignancy (Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 7 and 8).

**Table 2. Randomized, Controlled Studies With Decreased Survival and/or Decreased Locoregional Control**

Study/Tumor/(n)	Hemoglobin Target	Achieved Hemoglobin (Median; Q1, Q3*)	Primary Efficacy Outcome	Adverse Outcome for ESA-containing Arm
<b>Chemotherapy</b>				
<b>Study 1</b> Metastatic breast cancer (n = 939)	12-14 g/dL	12.9 g/dL; 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
<b>Study 2</b> Lymphoid malignancy (n = 344)	13-15 g/dL (M) 13-14 g/dL (F)	11 g/dL; 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
<b>Study 3</b> Early breast cancer (n = 733)	12.5-13 g/dL	13.1 g/dL; 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
<b>Study 4</b> Cervical cancer (n = 114)	12-14 g/dL	12.7 g/dL; 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and locoregional control
<b>Radiotherapy Alone</b>				
<b>Study 5</b> Head and neck cancer (n = 351)	≥ 15 g/dL (M) ≥ 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival
<b>Study 6</b> Head and neck cancer (n = 522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
<b>No Chemotherapy or Radiotherapy</b>				
<b>Study 7</b> Non-small cell lung cancer (n = 70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
<b>Study 8</b> Non-myeloid malignancy (n = 989)	12-13 g/dL	10.6 g/dL; 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

\*Q1= 25<sup>th</sup> percentile  
Q3= 75<sup>th</sup> percentile

### Decreased Overall Survival

Study 1 was described in the previous section [see *Warnings and Precautions (5.1)*]. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator-assessed time to tumor progression was not different between the 2 groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Study 2 was a randomized, double-blind study (darbepoetin alfa vs. placebo) conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Study 7 was a multicenter, randomized, double-blind study (epoetin alfa vs. placebo) in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 patients (planned accrual 300 patients), a significant difference in survival in favor of the patients in the placebo arm of the study was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Study 8 was a randomized, double-blind study (darbepoetin alfa vs. placebo) in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group than in the placebo group (8 months vs. 10.8 months; HR 1.30, 95% CI: 1.07, 1.57).

### Decreased Progression-free Survival and Overall Survival

Study 3 was a randomized, open-label, controlled, factorial design study in which darbepoetin alfa was administered to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years. The 3-year survival rate was lower (86% vs. 90%; HR 1.42, 95% CI: 0.93, 2.18) and the 3-year relapse-free survival rate was lower (72% vs. 78%; HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Study 4 was a randomized, open-label, controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to RBC transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic adverse reactions in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%; HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%; HR 1.28, 95% CI: 0.68, 2.42).

Study 5 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins  $\geq 14$  and  $\geq 15$  g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p = 0.0008) with medians of 406 days and 745 days in the epoetin beta and placebo arms, respectively. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

### Decreased Locoregional Control

Study 6 was a randomized, open-label, controlled study conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy alone (no chemotherapy) who were randomized to receive darbepoetin alfa to maintain hemoglobin levels of 14 to 15.5 g/dL or no darbepoetin alfa. An interim analysis performed on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

#### **5.4 Hypertension**

Epogen is contraindicated in patients with uncontrolled hypertension. Following initiation and titration of Epogen, approximately 25% of patients on dialysis required initiation of or increases in antihypertensive therapy; hypertensive encephalopathy and seizures have been reported in patients with CKD receiving Epogen.

Appropriately control hypertension prior to initiation of and during treatment with Epogen. Reduce or withhold Epogen if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions [see *Patient Counseling Information* (17)].

#### **5.5 Seizures**

Epogen increases the risk of seizures in patients with CKD. During the first several months following initiation of Epogen, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms or change in seizure frequency.

#### **5.6 Lack or Loss of Hemoglobin Response to Epogen**

For lack or loss of hemoglobin response to Epogen, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA [see *Warnings and Precautions* (5.7)]. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to Epogen therapy [see *Dosage and Administration* (2.2)].

#### **5.7 Pure Red Cell Aplasia**

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Epogen. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Epogen is not approved).

If severe anemia and low reticulocyte count develop during treatment with Epogen, withhold Epogen and evaluate patients for neutralizing antibodies to erythropoietin. Contact Amgen (1-800-77-AMGEN) to perform assays for binding and neutralizing antibodies. Permanently discontinue Epogen in patients who develop PRCA following treatment with Epogen or other erythropoietin protein drugs. Do not switch patients to other ESAs.

#### **5.8 Serious Allergic Reactions**

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Epogen. Immediately and permanently discontinue Epogen and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

#### **5.9 Albumin (Human)**

Epogen contains albumin, a derivative of human blood [see *Description* (11)]. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

## 5.10 Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of Epogen. Patients receiving Epogen may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

## 5.11 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during Epogen treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% [see *Dosage and Administration (2.1)*]. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism [see *Warnings and Precautions (5.1)*]
- Increased mortality and/or increased risk of tumor progression or recurrence in Patients With Cancer [see *Warnings and Precautions (5.3)*]
- Hypertension [see *Warnings and Precautions (5.4)*]
- Seizures [see *Warnings and Precautions (5.5)*]
- PRCA [see *Warnings and Precautions (5.7)*]
- Serious allergic reactions [see *Warnings and Precautions (5.8)*]

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

#### Patients with Chronic Kidney Disease

##### *Adult Patients*

Three double-blind, placebo-controlled studies, including 244 patients with CKD on dialysis, were used to identify the adverse reactions to Epogen. In these studies, the mean age of patients was 48 years (range: 20 to 80 years). One hundred and thirty-three (55%) patients were men. The racial distribution was as follows: 177 (73%) patients were white, 48 (20%) patients were black, 4 (2%) patients were Asian, 12 (5%) patients were other, and racial information was missing for 3 (1%) patients.

Two double-blind, placebo-controlled studies, including 210 patients with CKD not on dialysis, were used to identify the adverse reactions to Epogen. In these studies, the mean age of patients was 57 years (range: 24 to 79 years). One hundred and twenty-one (58%) patients were men. The racial distribution was as follows: 164 (78%) patients were white, 38 (18%) patients were black, 3 (1%) patients were Asian, 3 (1%) patients were other, and racial information was missing for 2 (1%) patients.

The adverse reactions with a reported incidence of  $\geq 5\%$  in Epogen-treated patients and that occurred at a  $\geq 1\%$  higher frequency than in placebo-treated patients are shown in the table below:

**Table 3. Adverse Reactions in Patients With CKD on Dialysis**

<b>Adverse Reaction</b>	<b>Epogen-treated Patients (n = 148)</b>	<b>Placebo-treated Patients (n = 96)</b>
Hypertension	27.7%	12.5%
Arthralgia	16.2%	3.1%
Muscle spasm	7.4%	6.3%
Pyrexia	10.1%	8.3%
Dizziness	9.5%	8.3%
Medical Device Malfunction (artificial kidney clotting during dialysis)	8.1%	4.2%
Vascular Occlusion (vascular access thrombosis)	8.1%	2.1%
Upper respiratory tract infection	6.8%	5.2%

An additional serious adverse reaction that occurred in less than 5% of epoetin alfa-treated dialysis patients and greater than placebo was thrombosis (2.7% Epogen and 1% placebo) [see *Warnings and Precautions (5.1)*].

The adverse reactions with a reported incidence of  $\geq 5\%$  in Epogen-treated patients and that occurred at a  $\geq 1\%$  higher frequency than in placebo-treated patients are shown in the table below:

**Table 4. Adverse Reactions in Patients With CKD Not on Dialysis**

<b>Adverse Reactions</b>	<b>Epogen-treated Patients (n = 131)</b>	<b>Placebo-treated Patients (n = 79)</b>
Hypertension	13.7%	10.1%
Arthralgia	12.2%	7.6%

Additional serious adverse reactions that occurred in less than 5% of epoetin alfa-treated patients not on dialysis and greater than placebo were erythema (0.8% Epogen and 0% placebo) and myocardial infarction (0.8% Epogen and 0% placebo) [see *Warnings and Precautions (5.1)*].

#### *Pediatric Patients*

In pediatric patients with CKD on dialysis, the pattern of adverse reactions was similar to that found in adults.

#### Zidovudine-treated HIV-infected Patients

A total of 297 zidovudine-treated HIV-infected patients were studied in 4 placebo-controlled studies. A total of 144 (48%) patients were randomly assigned to receive Epogen and 153 (52%) patients were randomly assigned to receive placebo. Epogen was administered at doses between 100 and 200 Units/kg 3 times weekly subcutaneously for up to 12 weeks.

For the combined Epogen treatment groups, a total of 141 (98%) men and 3 (2%) women between the ages of 24 and 64 years were enrolled. The racial distribution of the combined Epogen treatment groups was as follows: 129 (90%) white, 8 (6%) black, 1 (1%) Asian, and 6 (4%) other.

In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse reactions with an incidence of  $\geq 1\%$  in patients treated with Epogen were:

**Table 5. Adverse Reactions in Zidovudine-treated HIV-infected Patients**

Adverse Reaction	Epogen (n = 144)	Placebo (n = 153)
Pyrexia	42%	34%
Cough	26%	14%
Rash	19%	7%
Injection site irritation	7%	4%
Urticaria	3%	1%
Respiratory tract congestion	1%	Not reported
Pulmonary embolism	1%	Not reported

**Cancer Patients on Chemotherapy**

The data below were obtained in Study C1, a 16-week, double-blind, placebo-controlled study that enrolled 344 patients with anemia secondary to chemotherapy. There were 333 patients who were evaluable for safety; 168 of 174 patients (97%) randomized to Epogen received at least 1 dose of study drug, and 165 of 170 patients (97%) randomized to placebo received at least 1 placebo dose. For the once weekly Epogen-treatment group, a total of 76 men (45%) and 92 women (55%) between the ages of 20 and 88 years were treated. The racial distribution of the Epogen-treatment group was 158 white (94%) and 10 black (6%). Epogen was administered once weekly for an average of 13 weeks at a dose of 20,000 to 60,000 IU subcutaneously (mean weekly dose was 49,000 IU).

The adverse reactions with a reported incidence of  $\geq 5\%$  in Epogen-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

**Table 6. Adverse Reactions in Cancer Patients**

Adverse Reaction	Epogen (n = 168)	Placebo (n = 165)
Nausea	35%	30%
Vomiting	20%	16%
Myalgia	10%	5%
Arthralgia	10%	6%
Stomatitis	10%	8%
Cough	9%	7%
Weight decrease	9%	5%
Leukopenia	8%	7%
Bone pain	7%	4%
Rash	7%	5%
Hyperglycemia	6%	4%
Insomnia	6%	2%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%

**Surgery Patients**

Four hundred sixty-one patients undergoing major orthopedic surgery were studied in a placebo-controlled study (S1) and a comparative dosing study (2 dosing regimens, S2). A total of 358 patients were randomly assigned to receive Epogen and 103 (22%) patients were randomly assigned to receive placebo. Epogen was administered daily at a dose of 100 to 300 IU/kg subcutaneously for 15 days or at 600 IU/kg once weekly for 4 weeks.

For the combined Epogen treatment groups, a total of 90 (25%) and 268 (75%) women between the ages of 29 and 89 years were enrolled. The racial distribution of the combined Epogen treatment groups was as follows: 288 (80%) white, 64 (18%) black, 1 (< 1%) Asian, and 5 (1%) other.

The adverse reactions with a reported incidence of  $\geq 1\%$  in Epogen-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

**Table 7. Adverse Reactions in Surgery Patients**

Adverse Reaction	Study S1			Study S2	
	Epogen 300 U/kg (n = 112) <sup>a</sup>	Epogen 100 U/kg (n = 101) <sup>a</sup>	Placebo (n = 103) <sup>a</sup>	Epogen 600 U/kg x 4 weeks (n = 73) <sup>b</sup>	Epogen 300 U/kg x 15 days (n = 72) <sup>b</sup>
Nausea	47%	43%	45%	45%	56%
Vomiting	21%	12%	14%	19%	28%
Pruritus	16%	16%	14%	12%	21%
Headache	13%	11%	9%	10%	18%
Injection site pain	13%	9%	8%	12%	11%
Chills	7%	4%	1%	1%	0%
Deep vein thrombosis	6%	3%	3%	0% <sup>c</sup>	0% <sup>c</sup>
Cough	5%	4%	0%	4%	4%
Hypertension	5%	3%	5%	5%	6%
Rash	2%	2%	1%	3%	3%
Edema	1%	2%	2%	1%	3%

<sup>a</sup>Study included patients undergoing orthopedic surgery treated with Epogen or placebo for 15 days.

<sup>b</sup>Study included patients undergoing orthopedic surgery treated with Epogen 600 U/kg weekly for 4 weeks or 300 U/kg daily for 15 days.

<sup>c</sup>DVTs were determined by clinical symptoms.

## 6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during postmarketing use of Epogen:

- Seizures [see *Warnings and Precautions* (5.5)]
- PRCA [see *Warnings and Precautions* (5.7)]
- Serious allergic reactions [see *Warnings and Precautions* (5.8)]
- Injection site reactions, including irritation and pain
- Porphyria

## 6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to epoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) [see *Warnings and Precautions* (5.7)].

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Epogen with the incidence of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Epogen.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

The multidose vials are formulated with benzyl alcohol. Do not administer Epogen from multidose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to pregnant women. When therapy with Epogen is needed during pregnancy, use a benzyl alcohol-free formulation [*see Dosage and Administration (2) and Contraindications (4)*].

#### Pregnancy Category C (single-dose vials only)

There are no adequate and well-controlled studies of Epogen use during pregnancy. There are limited data on Epogen use in pregnant women. In animal reproductive and developmental toxicity studies, adverse fetal effects occurred when pregnant rats received epoetin alfa at doses approximating the clinical recommended starting doses. Single-dose formulations of Epogen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are reports of at least 33 pregnant women with anemia alone or anemia associated with severe renal disease and other hematologic disorders who received Epogen. Polyhydramnios and intrauterine growth restriction were reported in women with chronic renal disease, which is associated with an increased risk for these adverse pregnancy outcomes. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester. Due to the limited number of exposed pregnancies and multiple confounding factors (such as underlying maternal conditions, other maternal medications, and gestational timing of exposure), these published case reports and studies do not reliably estimate the frequency or absence of adverse outcomes.

When healthy rats received Epogen at doses of 100 Units/kg/day during mating and through early pregnancy (dosing stopped prior to organogenesis), there were slight increases in the incidences of pre- and post-implantation loss, and a decrease in live fetuses. This animal dose level of 100 Units/kg/day may approximate the clinical recommended starting dose, depending on the treatment indication. When healthy pregnant rats and rabbits received intravenous doses of up to 500 mg/kg/day of Epogen only during organogenesis, no teratogenic effects were observed in the offspring.

When healthy pregnant rats received Epogen at doses of 500 Units/kg/day late in pregnancy (after the period of organogenesis), offspring had decreased number of caudal vertebrae and growth delays [*see Nonclinical Toxicology (13.3)*].

Women who become pregnant during Epogen treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

### 8.3 Nursing Mothers

The multidose vials of Epogen are formulated with benzyl alcohol. Do not administer Epogen from multidose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to a nursing woman. When therapy with Epogen is needed in nursing women, use a benzyl alcohol-free formulation [*see Dosage and Administration (2) and Contraindications (4)*].

It is not known whether Epogen is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Epogen from single-dose vials is administered to a nursing woman.

## 8.4 Pediatric Use

The multidose vials are formulated with benzyl alcohol. Do not administer Epogen from multidose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to neonates or infants. When therapy with Epogen is needed in neonates and infants, use a benzyl alcohol-free formulation [*see Dosage and Administration (2) and Contraindications (4)*].

Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gaspings syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gaspings syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

### Pediatric Patients on Dialysis

Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established [*see Clinical Studies (14.1)*].

The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CKD [*see Warnings and Precautions (5) and Adverse Reactions (6.1)*].

### Pediatric Cancer Patients on Chemotherapy

Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established [*see Clinical Studies (14.3)*]. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer [*see Warnings and Precautions (5) and Adverse Reactions (6.1)*].

### Pediatric Patients With HIV Infection Receiving Zidovudine

Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

### Pharmacokinetics in Neonates

Limited pharmacokinetic data from a study of 7 preterm, very low birth weight neonates and 10 healthy adults given intravenous erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

## 8.5 Geriatric Use

Of the 4553 patients who received Epogen in the 6 studies for treatment of anemia due to CKD not receiving dialysis, 2726 (60%) were age 65 years and over, while 1418 (31%) were 75 years and over. Of the 757 patients who received Epogen in the 3 studies of CKD patients on dialysis, 361 (47%) were age 65 years and over, while

100 (13%) were 75 years and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hemoglobin [*see Dosage and Administration (2)*].

Among 778 patients enrolled in the 3 clinical studies of Epogen for the treatment of anemia due to concomitant chemotherapy, 419 received Epogen and 359 received placebo. Of the 419 who received Epogen, 247 (59%) were age 65 years and over, while 78 (19%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for Epogen in geriatric and younger patients within the 3 studies were similar.

Among 1731 patients enrolled in the 6 clinical studies of Epogen for reduction of allogeneic RBC transfusions in patients undergoing elective surgery, 1085 received Epogen and 646 received placebo or standard of care treatment. Of the 1085 patients who received Epogen, 582 (54%) were age 65 years and over, while 245 (23%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for Epogen in geriatric and younger patients within the 4 studies using the 3 times weekly schedule and 2 studies using the weekly schedule were similar.

Insufficient numbers of patients age 65 years or older were enrolled in clinical studies of Epogen for the treatment of zidovudine in HIV-infected patients to determine whether they respond differently from younger patients.

## **10 OVERDOSAGE**

Epogen overdose can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of Epogen dosage and/or with phlebotomy, as clinically indicated [*see Pharmacodynamics (12.2)*]. Cases of severe hypertension have been observed following overdose with ESAs [*see Warnings and Precautions (5.4)*].

## **11 DESCRIPTION**

Epogen (epoetin alfa) is a 165-amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology. It has a molecular weight of approximately 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

Epogen is formulated as a sterile, colorless liquid in vials in multiple formulations. Single-dose vials, formulated with an isotonic sodium chloride/sodium citrate-buffered solution, are supplied in multiple strengths. Each 1 mL vial contains 2000, 3000, 4000, or 10,000 Units of epoetin alfa, Albumin (Human) (2.5 mg), citric acid (0.06 mg), sodium chloride (5.9 mg), and sodium citrate (5.8 mg) in Water for Injection, USP (pH 6.9 ± 0.3). Single-dose 1 mL vials formulated with an isotonic sodium chloride/sodium phosphate buffer contain 40,000 Units of epoetin alfa albumin (human) (2.5 mg), citric acid (0.0068 mg), sodium chloride (5.8 mg), sodium citrate (0.7 mg), sodium phosphate dibasic anhydrate (1.8 mg), and sodium phosphate monobasic monohydrate (1.2 mg) in Water for Injection, USP (pH 6.9 ± 0.3). Multidose, 2 mL vials contain 10,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), and sodium citrate (1.3 mg) per 1 mL Water for Injection, USP (pH 6.1 ± 0.3). Multidose 1 mL vials contain 20,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), citric acid (0.11 mg), and sodium citrate (1.3 mg), per 1 mL in Water for Injection, USP (pH 6.1 ± 0.3).

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Epogen stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

### **12.2 Pharmacodynamics**

Epogen increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of Epogen administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly.

### 12.3 Pharmacokinetics

In adult and pediatric patients with CKD, the elimination half-life ( $t_{1/2}$ ) of plasma erythropoietin after intravenous administration of Epogen ranged from 4 to 13 hours. After subcutaneous administration,  $C_{max}$  was achieved within 5 to 24 hours. The  $t_{1/2}$  in adult patients with serum creatinine greater than 3 mg/dL was similar between those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in Epogen  $t_{1/2}$  among adult patients above or below 65 years of age.

A pharmacokinetic study comparing 150 Units/kg subcutaneous 3 times weekly to 40,000 Units subcutaneous weekly dosing regimen was conducted for 4 weeks in healthy subjects ( $n = 12$ ) and for 6 weeks in anemic cancer patients ( $n = 32$ ) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher  $C_{max}$  (3- to 7-fold), longer  $T_{max}$  (2- to 3-fold), higher  $AUC_{0-168h}$  (2- to 3-fold) of erythropoietin and lower clearance (CL) (50%) than the 150 Units/kg 3 times weekly regimen. In anemic cancer patients, the average  $t_{1/2}$  was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of  $T_{max}$  and CL were similar ( $13.3 \pm 12.4$  vs.  $14.2 \pm 6.7$  hours, and  $20.2 \pm 15.9$  vs.  $23.6 \pm 9.5$  mL/hr/kg) between week 1 when patients were receiving chemotherapy ( $n = 14$ ) and week 3 when patients were not receiving chemotherapy ( $n = 4$ ). Differences were observed after the 40,000 Units weekly dosing with longer  $T_{max}$  ( $38 \pm 18$  hours) and lower CL ( $9.2 \pm 4.7$  mL/hr/kg) during week 1 when patients were receiving chemotherapy ( $n = 18$ ) compared with those ( $22 \pm 4.5$  hours,  $13.9 \pm 7.6$  mL/hr/kg, respectively) during week 3 when patients were not receiving chemotherapy ( $n = 7$ ).

The pharmacokinetic profile of Epogen in children and adolescents appeared similar to that of adults.

The pharmacokinetics of Epogen has not been studied in patients with HIV infection.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenicity

The carcinogenic potential of Epogen has not been evaluated.

#### Mutagenicity

Epogen was not mutagenic or clastogenic under the conditions tested: Epogen was negative in the *in vitro* bacterial reverse mutation assay (Ames test), in the *in vitro* mammalian cell gene mutation assay (the hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus), in an *in vitro* chromosomal aberration assay in mammalian cells, and in the *in vivo* mouse micronucleus assay.

#### Impairment of Fertility

When administered intravenously to male and female rats prior to and during mating, and to females through the beginning of implantation (up to gestational day 7; dosing stopped prior to the beginning of organogenesis), doses of 100 and 500 Units/kg/day of Epogen caused slight increases in pre-implantation loss, post-implantation loss and decreases in the incidence of live fetuses. It is not clear whether these effects reflect a drug effect on the uterine environment or on the conceptus. This animal dose level of 100 Units/kg/day approximates the clinical recommended starting dose, depending on the patient's treatment indication, but may be lower than the clinical dose in patients whose doses have been adjusted.

### 13.3 Reproductive and Developmental Toxicology

When pregnant rats were administered intravenous Epogen, 500 Units/kg/day, after the period of organogenesis (from day 17 of gestation through day 21 of lactation), their pups exhibited decreased number of caudal vertebrae, decreased body weight gain, and delayed appearance of abdominal hair, eyelid opening, and ossification. This animal dose level of 500 Units/kg/day is approximately 5-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication.

When Epogen was administered intravenously during the period of organogenesis to pregnant rats (gestational days 7 to 17) and pregnant rabbits (gestational days 6 to 18), no evidence of teratogenic outcome was observed at the doses tested, up to 500 Units/kg/day. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no Epogen-related effects were apparent for their offspring (F2 generation fetuses).

## 14 CLINICAL STUDIES

### 14.1 Patients With Chronic Kidney Disease

#### Adult Patients on Dialysis

*Patients with chronic kidney disease on dialysis: ESA effects on rates of transfusion*

In clinical studies of CKD patients on dialysis, Epogen increased hemoglobin levels and decreased the need for RBC transfusion. Overall, more than 95% of patients were RBC transfusion-independent after receiving Epogen for 3 months. In clinical studies at starting doses of 50 to 150 Units/kg 3 times weekly, adult patients responded with an average rate of hemoglobin rise as presented in Table 8.

**Table 8: Average Rate of Hemoglobin Rise in 2 Weeks**

<b>Starting Dose (3 Times Weekly Intravenously)</b>	<b>Hemoglobin Increase in 2 Weeks</b>
50 Units/kg	0.5 g/dL
100 Units/kg	0.8 g/dL
150 Units/kg	1.2 g/dL

The safety and efficacy of Epogen were evaluated in 13 clinical studies involving intravenous administration to a total of 1010 anemic patients on dialysis. Overall, more than 90% of the patients treated with Epogen experienced improvement in hemoglobin concentrations. In the 3 largest of these clinical studies, the median maintenance dose necessary to maintain the hemoglobin between 10 to 12 g/dL was approximately 75 Units/kg 3 times weekly. More than 95% of patients were able to avoid RBC transfusions. In the largest US multicenter study, approximately 65% of the patients received doses of 100 Units/kg 3 times weekly or less to maintain their hemoglobin at approximately 11.7 g/dL. Almost 10% of patients received a dose of 25 Units/kg or less, and approximately 10% received a dose of more than 200 Units/kg 3 times weekly to maintain their hemoglobin at this level.

In the Normal Hematocrit Study, the yearly transfusion rate was 51.5% in the lower hemoglobin group (10 g/dL) and 32.4% in the higher hemoglobin group (14 g/dL).

#### *Other ESA trials*

In a 26-week, double-blind, placebo-controlled study, 118 patients on dialysis with an average hemoglobin of approximately 7 g/dL were randomized to either Epogen or placebo. By the end of the study, average hemoglobin increased to approximately 11 g/dL in the Epogen-treated patients and remained unchanged in patients receiving placebo. Epogen-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that were maintained throughout the study.

A multicenter, unit-dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered Epogen subcutaneously. Patients responded to Epogen administered subcutaneously in a manner similar to patients receiving intravenous administration.

### Pediatric Patients on Dialysis

The safety and efficacy of Epogen were studied in a placebo-controlled, randomized study of 113 children with anemia (hemoglobin  $\leq$  9 g/dL) undergoing peritoneal dialysis or hemodialysis. The initial dose of Epogen was 50 Units/kg intravenously or subcutaneously 3 times weekly. The dose of study drug was titrated to achieve either a hemoglobin of 10 to 12 g/dL or an absolute increase in hemoglobin of 2 g/dL over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hemoglobin (3.1 g/dL vs. 0.3 g/dL) was observed only in the Epogen arm. The proportion of children achieving a hemoglobin of 10 g/dL, or an increase in hemoglobin of 2 g/dL over baseline, at any time during the first 12 weeks was higher in the Epogen arm (96% vs. 58%). Within 12 weeks of initiating Epogen therapy, 92.3% of the pediatric patients were RBC transfusion independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of Epogen, hemodialysis patients received a higher median maintenance dose [167 Units/kg/week (n = 28) vs. 76 Units/kg/week (n = 36)] and took longer to achieve a hemoglobin of 10 to 12 g/dL (median time to response 69 days vs. 32 days) than patients undergoing peritoneal dialysis.

### Adult Patients With CKD Not Requiring Dialysis

Four clinical studies were conducted in patients with CKD not on dialysis involving 181 patients treated with Epogen. These patients responded to Epogen therapy in a manner similar to that observed in patients on dialysis. Patients with CKD not on dialysis demonstrated a dose-dependent and sustained increase in hemoglobin when Epogen was administered by either an intravenous or subcutaneous route, with similar rates of rise of hemoglobin when Epogen was administered by either route.

#### *Patients with chronic kidney disease not on dialysis: ESA effects on rates of transfusion*

In TREAT, a randomized, double-blind trial of 4038 patients with CKD and type 2 diabetes not on dialysis, a post-hoc analysis showed that the proportion of patients receiving RBC transfusions was lower in patients administered an ESA to target a hemoglobin of 13 g/dL compared to the control arm in which an ESA was administered intermittently if hemoglobin concentration decreased to less than 9 g/dL (15% versus 25%, respectively). In CHOIR, a randomized open-label study of 1432 patients with CKD not on dialysis, use of epoetin alfa to target a higher (13.5 g/dL) versus lower (11.3 g/dL) hemoglobin goal did not reduce the use of RBC transfusions. In each trial, no benefits occurred for the cardiovascular or end-stage renal disease outcomes. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile [*see Warnings and Precautions (5.1)*].

### ESA Effects on rates of death and other serious cardiac adverse events

Three randomized outcome trials (Normal Hematocrit Study [NHS], Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease [CHOIR], and Trial of Darbepoetin Alfa in Type 2 Diabetes and CKD [TREAT]) have been conducted in patients with CKD using Epogen/PROCRIT/Aranesp to target higher vs. lower hemoglobin levels. Though these trials were designed to establish a cardiovascular or renal benefit of targeting higher hemoglobin levels, in all 3 studies, patients randomized to the higher hemoglobin target experienced worse cardiovascular outcomes and showed no reduction in progression to ESRD. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile [*see Warnings and Precautions (5.1)*].

## **14.2 Zidovudine-treated Patients With HIV Infection**

The safety and efficacy of Epogen were evaluated in 4 placebo-controlled studies enrolling 297 anemic patients (hemoglobin < 10 g/dL) with HIV infection receiving concomitant therapy with zidovudine. In the subgroup of patients (89/125 Epogen and 88/130 placebo) with pre-study endogenous serum erythropoietin levels

≤ 500 mUnits/mL, Epogen reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group. Among those patients who required RBC transfusions at baseline, 43% of patients treated with Epogen versus 18% of placebo-treated patients were RBC transfusion-independent during the second and third months of therapy. Epogen therapy also resulted in significant increases in hemoglobin in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant reduction ( $p < 0.003$ ) in RBC transfusion requirements in patients treated with Epogen ( $n = 51$ ) compared to placebo-treated patients ( $n = 54$ ) whose mean weekly zidovudine dose was ≤ 4200 mg/week.

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving Epogen in doses from 100 to 200 Units/kg 3 times weekly achieved a hemoglobin of 12.7 g/dL without administration of RBC transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose pre-study endogenous serum erythropoietin levels were > 500 mUnits/mL, Epogen therapy did not reduce RBC transfusion requirements or increase hemoglobin compared to the corresponding responses in placebo-treated patients.

### 14.3 Cancer Patients on Chemotherapy

The safety and effectiveness of Epogen was assessed in two multicenter, randomized (1:1), placebo-controlled, double-blind studies (Study C1 and Study C2) and a pooled analysis of six additional randomized (1:1), multicenter, placebo-controlled, double-blind studies. All studies were conducted in patients with anemia due to concomitantly administered cancer chemotherapy. Study C1 enrolled 344 adult patients, Study C2 enrolled 222 pediatric patients, and the pooled analysis contained 131 patients randomized to epoetin alfa or placebo. In Studies C1 and C2, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion, from week 5 through end of the study, with the last-known RBC transfusion status carried forward for patients who discontinued treatment. In the pooled analysis, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion from week 5 through end of the study in the subset of patients who were remaining on therapy for 6 or more weeks.

#### Study C1

Study C1 was conducted in anemic patients (hemoglobin < 11.5 g/dL for males; < 10.5 g/dL for females) with non-myeloid malignancies receiving myelosuppressive chemotherapy. Randomization was stratified by type of malignancy (lung vs. breast vs. other), concurrent radiation therapy planned (yes or no), and baseline hemoglobin (< 9 g/dL vs. ≥ 9 g/dL); patients were randomized to epoetin alfa 40,000 Units ( $n = 174$ ) or placebo ( $n = 170$ ) as a weekly subcutaneous injection commencing on the first day of the chemotherapy cycle.

Ninety-one percent of patients were white, 44% were male, and the median age of patients was 66 years (range: 20 to 88 years). The proportion of patients withdrawn from the study prior to week 5 was less than 10% for placebo-treated or epoetin-treated patients. Per protocol, the last available hemoglobin values from patients who dropped out were included in the efficacy analyses. Efficacy results are shown in Table 9.

**Table 9. Study C1: Proportion of Patients Transfused**

Chemotherapy Regimen	Week 5 Through Week 16 or End of Study <sup>b</sup>	
	Epogen ( $n = 174$ )	Placebo ( $n = 170$ )
All Regimens	14% (25/174) <sup>a</sup>	28% (48/170)
Regimens without cisplatin	14% (21/148)	26% (35/137)
Regimens containing cisplatin	15% (4/26)	39% (13/33)

<sup>a</sup>Two-sided  $p < 0.001$ , logistic regression analysis adjusting for accrual rate and stratification variables

<sup>b</sup>Last-known RBC transfusion status carried forward for patients who discontinued treatment.

## Study C2

Study C2 was conducted in 222 anemic patients, ages 5 to 18, receiving chemotherapy for the treatment of various childhood malignancies. Randomization was stratified by cancer type (solid tumors, Hodgkin's disease, acute lymphocytic leukemia, vs. non-Hodgkin's lymphoma); patients were randomized to receive epoetin alfa at 600 Units/kg maximum 40,000 Units (n = 111) or placebo (n = 111) as a weekly intravenous injection.

Sixty-nine percent of patients were white, 55% were male, and the median age of patients was 12 years (range: 5 to 18 years). Two (2%) of placebo-treated patients and 3 (3%) of epoetin alfa-treated patients dropped out of the study prior to week 5. There were fewer RBC transfusions from week 5 through the end-of-study in epoetin-alfa treated patients [51% (57/111)] compared to placebo-treated patients [69% (77/111)]. There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy, or strength in patients receiving Epogen as compared to those receiving placebo.

## Pooled Analysis (Three Times Per Week Dosing)

The results of 6 studies of similar design and that randomized 131 patients to epoetin alfa or placebo were pooled to assess the safety and effectiveness of epoetin alfa. Patients were randomized to receive epoetin alfa at 150 Units/kg (n = 63) or placebo (n = 68), subcutaneously three times per week for 12 weeks in each study. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Twelve patients (19%) in the epoetin alfa arm and 10 patients (15%) in the placebo-arm dropped out prior to week 6 and are excluded from efficacy analyses.

**Table 10: Proportion of Patients Transfused in the Pooled Analysis for Three Times Per Week Dosing**

Chemotherapy Regimen	Week 5 Through Week 12 or End of Study <sup>b</sup>	
	Epogen	Placebo
All Regimens	22% (11/51) <sup>a</sup>	43% (25/58)
Regimens without cisplatin	21% (6/29)	33% (11/33)
Regimens containing cisplatin	23% (5/22)	56% (14/25)

<sup>a</sup>Two-sided p < 0.05, unadjusted

<sup>b</sup>Limited to patients remaining on study beyond week 6 and includes only RBC transfusions during weeks 5-12.

## 14.4 Surgery Patients

The safety and efficacy of Epogen were evaluated in a placebo-controlled, double-blind study (S1) enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require  $\geq 2$  units of blood and who were not able or willing to participate in an autologous blood donation program. Patients were stratified into 1 of 3 groups based on their pretreatment hemoglobin [ $\leq 10$  g/dL (n = 2),  $> 10$  to  $\leq 13$  g/dL (n = 96), and  $> 13$  to  $\leq 15$  g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg Epogen, 100 Units/kg Epogen, or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery. All patients received oral iron and a low-dose, postoperative warfarin regimen.

Treatment with Epogen 300 Units/kg significantly (p = 0.024) reduced the risk of allogeneic RBC transfusion in patients with a pretreatment hemoglobin of  $> 10$  to  $\leq 13$  g/dL; 5/31 (16%) of patients treated with Epogen 300 Units/kg, 6/26 (23%) of patients treated with Epogen 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused. There was no significant difference in the number of patients transfused between Epogen (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the  $> 13$  to  $\leq 15$  g/dL hemoglobin stratum. There were too few patients in the  $\leq 10$  g/dL group to determine if Epogen is useful in this hemoglobin strata. In the  $> 10$  to  $\leq 13$  g/dL pretreatment stratum, the mean number of units transfused per Epogen-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p = 0.028). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with Epogen.

Epogen was also evaluated in an open-label, parallel-group study (S2) enrolling 145 patients with a pretreatment hemoglobin level of  $\geq 10$  to  $\leq 13$  g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program. Patients were randomly assigned to receive 1 of 2 subcutaneous dosing regimens of Epogen (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery, and for 4 days after surgery). All patients received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than that observed in the 300 Units/kg daily group. The mean increase in absolute reticulocyte count was smaller in the weekly group ( $0.11 \times 10^6/\text{mm}^3$ ) compared to the daily group ( $0.17 \times 10^6/\text{mm}^3$ ). Mean hemoglobin levels were similar for the 2 treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar RBC transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group]. The mean number of units transfused per patient was approximately 0.3 units in both treatment groups.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Store at 36°F to 46°F (2°C to 8°C). Do not freeze.  
Do not shake. Protect from light; store Epogen in the carton until use.  
Do not use Epogen that has been shaken or frozen.

Single-dose, Preservative-free Vial (in citrate-buffered formulation): 1 mL of solution contains 2000 (NDC 55513-126-10), 3000 (NDC 55513-267-10), 4000 (NDC 55513-148-10), or 10,000 Units (NDC 55513-144-10) of epoetin alfa. Each strength is supplied in dispensing packs containing 10 single-dose vials.

Single-dose, Preservative-free Vial (in phosphate-buffered formulation): 1 mL of solution contains 40,000 Units (NDC 55513-823-10) of epoetin alfa and is supplied in dispensing packs containing 10 single-dose vials.

Multidose, Preserved Vial: 2 mL total volume (20,000 Units total; 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units (NDC 55513-283-10) of epoetin alfa, and is supplied in dispensing packs containing 10 multidose vials.

Multidose, Preserved Vial: 1 mL total volume (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units (NDC 55513-478-10) of epoetin alfa and is supplied in dispensing packs containing 10 multidose vials.

## 17 PATIENT COUNSELING INFORMATION

*See Medication Guide.*

Prior to treatment, inform patients of the risks and benefits of Epogen.

Inform patients with cancer that they must sign the patient-healthcare provider acknowledgment form before the start of each treatment course with Epogen and that healthcare providers must enroll and comply with the ESA APPRISE Oncology Program in order to prescribe Epogen.

Inform patients:

- To read the Medication Guide and to review and discuss any questions or concerns with their healthcare provider before starting Epogen and at regular intervals while receiving Epogen.
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression [see *Warnings and Precautions (5.1, 5.3)*].
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.
- Of the need to have regular laboratory tests for hemoglobin.

- Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers [*see Use in Specific Populations (8.1, 8.3, 8.4)*].

Instruct patients who self-administer Epogen of the:

- Importance of following the Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Proper disposal of used syringes, needles, and unused vials, and of the full container.

# AMGEN®

Epogen® (epoetin alfa)

**Manufactured by:**

Amgen Manufacturing Limited, a subsidiary of Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

This product, the process of its manufacture, or its use, may be covered by one or more U.S. Patents, including U.S. Patent No. 5,441,868; 5,547,933; 5,618,698; 5,756,349; and 5,955,422.

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## Procrit Oregon Medicare Guidelines

### State Medicare Guidelines / CMS 1500 Oregon

Legal Notice: This document is presented for informational purposes only and is not intended to provide reimbursement or legal advice. Laws, regulations and policies concerning reimbursement are complex and are updated frequently. While we have made an effort to be current as of the issue date of this document, the information may not be as current or comprehensive when you view it. Please consult with your counsel or reimbursement specialist for any reimbursement or billing questions.

Please refer to the **National Coverage Determination (NCD)** for additional information that may supercede the Medicare guidelines provided by your local Medicare Carrier, Fiscal Intermediary, or Medicare Administrative Contractor (MAC).

### Summary - Part A - Updated February 27, 2012

For additional information on Medicare-covered indications for your specific state, please see the appropriate Part A Local Coverage Determinations/Supporting Documentation, which may be accessed through the link above or by

Your state has two Medicare contractors which process claims for Part A providers. If you use WPS (formerly Mutual of Omaha), please select it now. **WPS** If you do not use WPS, the Medicare guideline summary is below.

Indication	ICD-9-CM	HCPCS	Starting Labs	Ending Labs	GFR/Serum Creatinine	Allowable Dosage	Post Chemo
Cancer (chemo)	285.3 and V67.2 or V58.11 Link	J0885 Link	Not Stated Link	Not Stated	SC: Not Applicable  GFR: Not Applicable	Not Stated	Not Stated
AIDS/AZT	285.9 and 042 Link	J0885 Link	HCT < 30% w/in one wk of initial treatment & anemia must be symptomatic Link	Hb 12 g/dL or HCT 36% Link	SC: Not Applicable  GFR: Not Applicable	Per FDA Link	Not Applicable
Renal	285.21 and 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.3, 585.4, 585.5, 585.9 or V42.0 Link	J0885 Link	HCT < 30% w/in one wk of the initial injection, or higher if anemia is symptomatic Link	HCT 36% Link	SC: Not Stated  GFR: GFR < 60 mL/min/1.73m <sup>2</sup> Link	Not Stated	Not Applicable
Surgery (hip or knee)	284.81, 284.89, 284.9, 285.21, 285.22, 285.29, 285.3, 285.8, or 285.9 and V07.8 Link	J0885 Link	Hb between 10 and 13 g/dL w/in one wk of initial injection Link	Not Stated	SC: Not Applicable  GFR: Not Applicable	Not Stated	Not Applicable

These summaries have been prepared using the Medicare guidelines. If you would like to receive the Medicare guidelines, you can call PROCritline® at 1-800-553-3851 or you can contact the Medicare contractor directly at the web address in the State Medicare Payers box above.

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Please refer to the **National Coverage Determination (NCD)** for additional information that may supercede the Medicare guidelines provided by your local Medicare Carrier, Fiscal Intermediary, or Medicare Administrative Contractor (MAC).

### Summary - Part B - Updated February 27, 2012

For additional information on Medicare-covered indications for your specific state, please see the appropriate Part B Local Coverage Determinations/Supporting Documentation, which may be accessed through the link above or by

Indication	ICD-9-CM	HCPCS	Starting Labs	Ending Labs	GFR/Serum Creatinine	Allowable Dosage	Post Chemo
Cancer (chemo)	285.3 and V67.2 or V58.11 Link	J0885 Link	Not Stated Link	Not Stated	SC: Not Applicable  GFR: Not Applicable	Not Stated	Not Stated

## Procrit Oregon Medicare Guidelines

AIDS/AZT	285.9 and 042 Link	J0885 Link	HCT < 30% w/in one wk of initial treatment & anemia must be symptomatic Link	Hb 12 g/dL or HCT 36% Link	SC: Not Applicable  GFR: Not Applicable	Per FDA Link	Not Applicable
Renal	285.21 and 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.3, 585.4, 585.5, 585.9 or V42.0 Link	J0885 Link	HCT < 30% w/in one wk of the initial injection, or higher if anemia is symptomatic Link	HCT 36% Link	SC: Not Stated  GFR: GFR < 60 mL/min/1.73m <sup>2</sup> Link	Not Stated	Not Applicable
Surgery (hip or knee)	284.81, 284.89, 284.9, 285.21, 285.22, 285.29, 285.3, 285.8, or 285.9 and V07.8 Link	J0885 Link	Hb between 10 and 13 g/dL w/in one wk of initial injection Link	Not Stated	SC: Not Applicable  GFR: Not Applicable	Not Stated	Not Applicable

These summaries have been prepared using the Medicare guidelines. If you would like to receive the Medicare guidelines, you can call PROCRIline<sup>®</sup> at 1-800-553-3851 or you can contact the Medicare contractor directly at the web address in the State Medicare Payers box above.

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### ▼ INDICATIONS AND IMPORTANT SAFETY INFORMATION

#### Indications for PROCRI<sup>®</sup> (Epoetin alfa)

##### Anemia Due to Chronic Kidney Disease

PROCRI<sup>®</sup> is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

##### Anemia Due to Zidovudine in HIV-infected Patients

PROCRI<sup>®</sup> is indicated for the treatment of anemia due to zidovudine administered at < 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of < 500 mUnits/mL.

##### Anemia Due to Chemotherapy in Patients With Cancer

PROCRI<sup>®</sup> is indicated for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

##### Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery

PROCRI<sup>®</sup> is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to < 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. PROCRI<sup>®</sup> is not indicated for patients who are willing to donate autologous blood pre-operatively.

PROCRI<sup>®</sup> has not been shown to improve quality of life, fatigue, or patient well-being.

PROCRI<sup>®</sup> is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

#### Important Safety Information for PROCRI<sup>®</sup> (Epoetin alfa)

**WARNINGS: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

##### *Chronic Kidney Disease:*

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest PROCRI<sup>®</sup> dose sufficient to reduce the need for red blood cell (RBC) transfusions.

##### *Cancer:*

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical

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studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.

- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology program to prescribe and/or dispense PROCRT<sup>®</sup> to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid red blood cell (RBC) transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

### *Perisurgery:*

- Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended.

(See WARNINGS AND PRECAUTIONS: Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism, WARNINGS AND PRECAUTIONS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)

### Contraindications

PROCRT<sup>®</sup> is contraindicated in patients with:

- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with PROCRT<sup>®</sup> or other erythropoietin protein drugs
- Serious allergic reactions to PROCRT<sup>®</sup>

PROCRT<sup>®</sup> from multidose vials contains benzyl alcohol and is contraindicated in:

- Neonates, infants, pregnant women, and nursing mothers. When therapy with PROCRT<sup>®</sup> is needed in neonates and infants, use single-dose vials; do not admix with bacteriostatic saline containing benzyl alcohol.

### Additional Important Safety Information

Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13-14 g/dL) to lower targets (9-11.3 g/dL), PROCRT<sup>®</sup> and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, PROCRT<sup>®</sup> and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer

- ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival. These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

Hypertension

- PROCRT<sup>®</sup> is contraindicated in patients with uncontrolled hypertension. Following initiation and titration of PROCRT<sup>®</sup>, approximately 25% of patients on dialysis required initiation of or increases in antihypertensive therapy; hypertensive encephalopathy and seizures have been reported in patients with CKD receiving PROCRT<sup>®</sup>.
- Appropriately control hypertension prior to initiation of and during treatment with PROCRT<sup>®</sup>. Reduce or withhold PROCRT<sup>®</sup> if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

Seizures

- PROCRT<sup>®</sup> increases the risk of seizures in patients with CKD. During the first several months following initiation of PROCRT<sup>®</sup>, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their health care practitioner for new-onset seizures, premonitory symptoms or change in seizure frequency.

Lack or Loss of Hemoglobin Response to PROCRT<sup>®</sup>

- For lack or loss of hemoglobin response to PROCRT<sup>®</sup>, initiate a search for causative factors (eg, iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to PROCRT<sup>®</sup> therapy.

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### Pure Red Cell Aplasia

- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with PROCRIT®. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which PROCRIT® is not approved).
- If severe anemia and low reticulocyte count develop during treatment with PROCRIT®, withhold PROCRIT® and evaluate patients for neutralizing antibodies to erythropoietin. Contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) to perform assays for binding and neutralizing antibodies. Permanently discontinue PROCRIT® in patients who develop PRCA following treatment with PROCRIT® or other erythropoietin protein drugs. Do not switch patients to other ESAs.

### Serious Allergic Reactions

- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with PROCRIT®. Immediately and permanently discontinue PROCRIT® and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

### Laboratory Monitoring

- Evaluate transferrin saturation and serum ferritin prior to and during PROCRIT® treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

PROCRIT® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

### Anemia in Patients with Chronic Kidney Disease Not on Dialysis

- Consider initiating PROCRIT® treatment only when the hemoglobin level is less than 10 g/dL and:
  - The patient's rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and
  - Reducing the risk of alloimmunization and/or other RBC transfusion related risks is a goal.
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of PROCRIT®, and use the lowest dose of PROCRIT® sufficient to reduce the need for RBC transfusions.
- When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.
  - Do not increase the dose more frequently than once every 4 weeks. Decreases in doses can occur more frequently. Avoid frequent dose adjustments.
  - If the hemoglobin rises rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose of PROCRIT® by 25% or more as needed to reduce rapid responses.
  - For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
  - For patients who do not respond adequately over a 12-week escalation period, increasing the PROCRIT® dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue PROCRIT® if responsiveness does not improve.
- Adverse reactions in > 5% of PROCRIT®-treated patients in clinical studies were hypertension and arthralgia.

### Chemotherapy-Induced Anemia

- PROCRIT® is not indicated for use in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- PROCRIT® is not indicated for use in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Initiate PROCRIT® in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.
- Use the lowest dose of PROCRIT® necessary to avoid RBC transfusions.
- Reduce dose by 25% if:
  - Hemoglobin increases greater than 1 g/dL in any 2-week period or
  - Hemoglobin reaches a level needed to avoid RBC transfusion.
- Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.
- Adverse reactions in > 5% of PROCRIT®-treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis.

### Surgery/Perisurgery

- PROCRIT® is not indicated for use in patients scheduled for surgery who are willing to donate autologous blood.
- PROCRIT® is not indicated for use in patients undergoing cardiac or vascular surgery.

## Procrit Oregon Medicare Guidelines

- Deep venous thrombosis prophylaxis is recommended during PROCRT® therapy.
- Adverse reactions in > 5% of PROCRT®-treated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension.

### Anemia in Zidovudine-treated HIV-infected Patients

- Withhold PROCRT® if hemoglobin exceeds 12 g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.
- Discontinue PROCRT® if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.
- Adverse reactions in > 5% of PROCRT®-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation.

Please see accompanying full Prescribing Information, including Boxed WARNINGS.  
Medication Guide for PROCRT®

Provide the Medication Guide to your patients and encourage discussion.

Patient Instructions for Use

Instructions if the patient or caregiver has been trained to give PROCRT® injections at home.

## **Section 6**

### **Straightforward Items**

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
92081  92082 92083	Visual field examination, unilateral or bilateral, with interpretation and report; limited examination Intermediate examination Extended examination	<b>435</b> MIGRAINE HEADACHES	DMAP is requesting that 92085 be added to line 435 to pair with 346.00 (Migraine with aura, without mention of intractable migraine without mention of status migrainosus). 92082 is on 50+ lines on the List. Similar codes 92081 and 92093 are on all lines as 92082. Visual field exams are noted as part of the work-up of ocular migraines in the medical literature.	Add 92081-3 to line 435
21076	Impression and custom preparation; surgical obturator prosthesis	<b>325</b> CLEFT PALATE AND/OR CLEFT LIP	DMAP is requesting that 21076 be added to line 325 to pair with 749.21 (Cleft palate with cleft lip; unilateral, complete). 21076 is currently on lines 273 DEFORMITIES OF HEAD and 514 ENOPHTHALMOS.	Add 21076 to line 325
67121	Removal of implanted material, posterior segment; intraocular	<b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 67121 be added to line 448 to pair with 996.53 (Mechanical complication of other specified prosthetic device, implant, and graft due to ocular lens prosthesis). 67121 is currently only on line 374 RETROLENTAL FIBROPLASIA.	Add 67121 to line 448

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
27030	Arthrotomy, hip, with drainage (eg, infection)	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 27030 be added to line 308 to pair with 996.66 (Infection and inflammatory reaction due to internal joint prosthesis). 27030 is currently only on line 161 PYOGENIC ARTHRITIS.	Add 27030 to line 308
69711	Removal or repair of electromagnetic bone conduction hearing device in temporal bone	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 69711 be added to line 308 to pair with 996.69 (Infection and inflammatory reaction due to other internal prosthetic device, implant, and graft). 69711 is currently on lines 448 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT and 590 CONDUCTIVE HEARING LOSS.	Add 69711 to line 308
36147 37207 75791	Introduction of needle and/or catheter, arteriovenous shunt created for dialysis (graft/fistula); initial access with complete radiological evaluation of dialysis access, including fluoroscopy Transcatheter placement of intravascular stent(s) (except coronary, carotid, vertebral, iliac and lower extremity arteries), open; initial vessel Angiography, arteriovenous shunt (eg, dialysis patient fistula/ graft), complete evaluation of dialysis access, including fluoroscopy	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 36147, 37207, and 75791 be added to line 308 to pair with 996.73 (Other complication of internal prosthetic device, implant, and graft; due to renal dialysis device, implant, and graft). 36147 and 75791 are currently on lines 66,138,235,352,366. 37207 is currently on lines 303,350,378,472. Per the literature, 37207 is used to treat “stenotic lesions of arteriovenous dialysis fistulas and grafts.”	Add 36147, 37207, and 75791 to line 308

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
43269	Endoscopic retrograde cholangiopancreatography (ERCP); with endoscopic retrograde removal of foreign body and/or change of tube or stent	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT <b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 43269 be added to line 308 to pair with 997.41 (Retained cholelithiasis following cholecystectomy) and to line 448 to pair with 996.59 (Mechanical complication due to other implant and internal device, not elsewhere classified). 43269 is currently on lines 61,200,267, 319, 341, 459, 671. 996.59 includes mechanical complication of prosthetic implant in the bile duct per ICD-9 coding.	Add 43269 to lines 308 and 448
57295	Revision (including removal) of prosthetic vaginal graft; open abdominal approach	<b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 43269 be added to line 448 to pair with 996.30 (Mechanical complication of unspecified genitourinary device, implant, and graft). 57395 is currently on line 308.	Add 57295 to line 448.
26432	Closed treatment of distal extensor tendon insertion, with or without percutaneous pinning (eg, mallet finger)	<b>550</b> DEFORMITIES OF UPPER BODY AND ALL LIMBS	DMAP is requesting that 26432 be added to line 550 to pair with 736.1 (Mallet finger). 26432 is currently on lines 216,308,406. 736.1 is also on line 407 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION.	Add 26432 to line 550

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
20661	Application of halo, including removal; cranial	<b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 20661 be added to line 448 to pair with 996.67 (Infection and inflammatory reaction due to other internal orthopedic device, implant, and graft). 20661 is currently on lines 158, 273, 400, and 562.	Add 20661 to line 448.
37224 37228 49429	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral; with transluminal angioplasty Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel; with transluminal angioplasty Removal of peritoneal-venous shunt	<b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 37224, 37228, and 49429 be added to line 448 to pair with 996.74 (Other complications due to other vascular device, implant, and graft). 37224 and 37228 are currently on line 378 ATHEROSCLEROSIS, PERIPHERAL. 49429 is currently on line 230 PORTAL VEIN THROMBOSIS. 996.74 includes complications due to stenosis, thrombus, occlusion NOS, embolism, etc.	Add 37224, 37228, and 49429 to line 448.
69424	Ventilating tube removal requiring general anesthesia	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 69424 be added to line 448 to pair with 996.79 (Other complications due to other internal prosthetic device, implant, and graft). 69424 is currently on lines 383,405,418,502.	Add 69424 to line 308

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
65920	Removal of implanted material, anterior segment of eye	<b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 65920 be added to line 448 to pair with 996.53 (Mechanical complication of other specified prosthetic device, implant, and graft; Due to ocular lens prosthesis). 65920 is currently on lines 308 and 337.	Add 65920 to line 448
63707 63709	Repair of dural/cerebrospinal fluid leak, not requiring laminectomy Repair of dural/cerebrospinal fluid leak or pseudomeningocele, with laminectomy.	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT <b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 63709 be added to line 308 to pair with 997.09 (Other nervous system complications) and to line 448 to pair with 349.31 (Accidental puncture or laceration of dura during a procedure). 63709 is currently only on line 40 SPINA BIFIDA. On review, 63707 was also found to be only on line 40. These procedures may be required if there are complications after a neurosurgical spinal procedure.	Add 63707 and 63709 to line 308 and 448
36822	Insertion of cannula(s) for prolonged extracorporeal circulation for cardiopulmonary insufficiency (ECMO)	<b>Ancillary List</b>	DMAP is requesting that 36822 be removed from lines 14, 98, 111, 154,248,310 and placed on the Ancillary List. All other ECMO codes (CPT 33960-33961) are currently located on the Ancillary List.	Remove 36822 from lines 14, 98, 111, 154, 248, and 310.  Advise DMAP to place 36822 on the Ancillary List.

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
27886	Amputation, leg, through tibia and fibula; re-amputation	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT <b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 27886 be added to line 308 to pair with 997.62 (Amputation stump complication; Infection (chronic)) and to line 448 to pair with 997.69 (Amputation stump complication; Other). 27886 is currently on lines 146, 190, 208, 250, 271, 346, 467, 308, and 448.	Add 27886 to lines 308 and 448
25909	Amputation, forearm, through radius and ulna; re-amputation	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT <b>448</b> COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 25909 be added to line 448 to pair with 997.69 (Amputation stump complication). 25909 is currently on lines 167, 190, 208, 250, 308, and 346. If added to line 448, 25909 should also be added to line 308 to pair with other amputation complications.	Add 25909 to line 308 and 448
21501	Incision and drainage, deep abscess or hematoma, soft tissues of neck or thorax	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 21501 be added to line 308 to pair with 998.51 (Infected postoperative seroma). 21501 is currently on lines 214 and 448.	Add 21501 to line 308
32120	Thoracotomy; for postoperative complications	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 32120 be added to line 308 to pair with 998.11 (Hemorrhage complicating a procedure). 32120 is currently on lines 63, 88, 307, and 409.	Add 32120 to line 308

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
15200  15201	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less; Each additional 20 sq cm	<b>197</b> CANCER OF BREAST	DMAP is requesting that 15200 be added to line 197 to pair with V10.3 (Personal history of malignant neoplasm; Breast) and with 174.9 (Malignant neoplasm of breast (female), unspecified). 15200 is currently on multiple lines. This procedure would like be used in reconstructive procedures.	Add 15200-1 to line 197
38542	Dissection, deep jugular node(s)	<b>221</b> NON-HODGKIN'S LYMPHOMAS	DMAP is requesting that 38542 be added to line 221 to pair with 202.71 (Peripheral T-cell Lymphoma, Lymph nodes of head, face, and neck). These codes currently pair—38542 is listed in the HERC database as being on line 221. However, it does not appear on the website posted List.	Affirm the placement of 38542 on line 221
51525	Cystotomy; for excision of bladder diverticulum, single or multiple	<b>351</b> FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	DMAP is requesting that 51525 be added to line 351 to pair with 596.3 (Diverticulum of bladder). 51525 is currently on line 96 CONGENITAL ANOMALIES OF URINARY SYSTEM.	Add 51525 to line 351

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
29425	Application of short leg cast (below knee to toes); walking or ambulatory type	<b>467</b> MALUNION AND NONUNION OF FRACTURE <b>536</b> CLOSED FRACTURE OF GREAT TOE <b>565</b> DEFORMITIES OF FOOT	DMAP is requesting that 29425 be added to line 565 to pair with 736.72 (Equinos deformity of foot, acquired), to line 536 to pair with V54.19 (Aftercare for healing traumatic fracture of other bone) and to line 467 to pair with 733.82 (Nonunion of fracture). 29425 is currently on lines 143, 297, 318, 382, 406, and 455.	Add 29425 to lines 467, 536 and 565
28300	Osteotomy; calcaneus (eg, Dwyer or Chambers type procedure), with or without internal fixation	<b>550</b> DEFORMITIES OF UPPER BODY AND ALL LIMBS	DMAP is requesting that 28300 be added to line 550 to pair with 736.79 (Other acquired deformities of ankle and foot; Other). 28300 is currently on lines 297,318,565.	Add 28300 to line 550
11982	Removal, non-biodegradable drug delivery implant	<b>308</b> COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 11982 be added to line 308 to pair with 998.59 (Other postoperative infection). 11982 is currently on lines 7,193,448.	Add 11982 to line 308
77418  77421	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session  Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation therapy	<b>218</b> CANCER OF UTERUS	DMAP is requesting that 77418 and 77421 be added to line 218 to pair with 182.0 (Malignant neoplasm of corpus uteri, except isthmus). 77418 and 77421 are on multiple lines.	Add 77418 and 77421 to line 218

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
97530	Therapeutic activities, direct (one-on-one) patient contact by the provider (use of dynamic activities to improve functional performance), each 15 minutes	<b>441</b> PERIPHERAL NERVE ENTRAPMENT	DMAP is requesting that 97530 be added to line 441 to pair with 354.2 (Lesion of ulnar nerve). 97530 is on many lines.	Add 97530 to line 441
34451	Thrombectomy, direct or with catheter; vena cava, iliac, femoropopliteal vein, by abdominal and leg incision	<b>303</b> BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS	DMAP is requesting that 34451 be added to line 303 to pair with 453.2 (Other venous embolism and thrombosis of inferior vena cava). 34451 is currently on line 163 ACUTE VASCULAR INSUFFICIENCY OF INTESTINE.	Add 34451 to line 303
45905 45910	Dilation of anal sphincter (separate procedure) under anesthesia other than local Dilation of rectal stricture (separate procedure) under anesthesia other than local	<b>111</b> CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION	DMAP is requesting that 45910 be added to line 111 to pair with 751.2 (Atresia and stenosis of large intestine, rectum, and anal canal). 45910 is currently on line 506 ANAL FISTULA; CHRONIC ANAL FISSURE. 45905 should also be added to line 111.	Add 45905 and 45910 to line 111
48545	Pancreatorrhaphy for injury	<b>88</b> INJURY TO INTERNAL ORGANS	DMAP is requesting that 48545 be added to line 88 to pair with 863.83 (Injury to pancreas tail, without mention of open wound into cavity). 48545 is currently on line 111.	Add 48545 to line 88

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
47350  47360	Management of liver hemorrhage; simple suture of liver wound or injury  Management of liver hemorrhage; complex suture of liver wound or injury, with or without hepatic artery ligation	<b>88</b> INJURY TO INTERNAL ORGANS	DMAP is requesting that 47350 be added to line 88 to pair with 864.05 (Liver injury without mention of open wound into cavity, unspecified laceration). 47350 are 47360 are currently on line 219 RUPTURE OF LIVER. Similar codes 47361-2 are on line 88 as well as line 219.	Add 47350 and 47360 to line 88
40830  40831	Closure of laceration, vestibule of mouth; 2.5 cm or less  Closure of laceration, vestibule of mouth; over 2.5 cm	<b>216</b> DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 40830 be added to line 216 to pair with 873.43 (Other open wound of lip without mention of complication). 40830 is on line 325 CLEFT PALATE AND/OR CLEFT LIP. 40831 is on lines 325 and 650.	Add 40830 and 40831 to line 216
35476	Transluminal balloon angioplasty, percutaneous; venous	<b>303</b> BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS	DMAP is requesting that 35476 be added to line 303 to pair with 453.82 (Acute venous embolism and thrombosis of deep veins of upper extremity). 35476 is on lines 303 and 378.	Add 35476 to line 303
27430	Quadricepsplasty (eg, Bennett or Thompson type)	<b>318</b> NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	DMAP is requesting that 27430 be added to line 318 to pair with 718.46 (Contracture of lower leg joint). 27430 is currently on lines 143,297,382,455.	Add 27430 to line 318

**Straightforward Issues—April, 2012**

<b>Code</b>	<b>Code Description</b>	<b>Line(s) Involved</b>	<b>Issue</b>	<b>Recommendation(s)</b>
25645	Open treatment of carpal bone fracture (other than carpal scaphoid [navicular]), each bone	<b>143</b> OPEN FRACTURE/DISLOCATION OF EXTREMITIES	DMAP is requesting that 25645 be added to line 143 to pair with 814.18 (Open fracture of hamate (cuciform) bone of wrist). 25645 is currently on line 382 CLOSED FRACTURE OF EXTREMITIES (EXCEPT TOES).	Add 25645 to line 143
62010	Elevation of depressed skull fracture; with repair of dura and/or debridement of brain.	<b>101</b> SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH LOSS OF CONSCIOUSNESS, COMPOUND/DEPRESSED FRACTURES OF SKULL	DMAP is requesting that 62010 be added to line 101 to pair with 801.90 (Open fracture of base of skull with intracranial injury of other and unspecified nature, unspecified state of consciousness). 62010 is currently on line 273 DEFORMITIES OF HEAD. Similar codes 62000 and 62005 (Elevation of depressed skull fracture) are on line 101.	Add 62010 to line 101  Remove 62010 from line 273

## Partial/Total Colectomy

Question: Where should partial colectomy codes appear on the Prioritized List?

Question source: DMAP, HERC staff

Issue: DMAP brought a pairing question to HERC staff, requesting pairing of 211.3 (Benign neoplasm of Colon) with laparoscopic partial colectomy (CPT 44204-8) as well as 44213 [Laparoscopic mobilization of splenic flexure performed in conjunction with partial colectomy (secondary code to 44204 family)]. On review of this question, HERC staff determined that the partial colectomy codes were on inconsistent lines.

211.3 is on line 173 ANAL, RECTAL AND COLONIC POLYPS, which does not contain any of the partial or total laparoscopic colectomy codes. All of the open partial and total colectomy codes (CPT 44140-44160) are on line 173. Occasionally, patients will have part or all of their colon removed for multiple polyps. Usual HSC/HERC policy is to add laparoscopic codes to any line with comparable open codes.

### Recommendations:

- 1) Changes as outlined in following table
  - a. Key: X presently on line, ~~X~~ add, ~~X~~ delete
  - b. Makes placement consistent
- 2) Add laparoscopic partial and complete colectomy CPT codes to line 173 ANAL, RECTAL AND COLONIC POLYPS
  - a. 44140-44160, 44204-44213

### Partial/Total Colectomy

CPT code	Code description	Line 35	Line 48	Line 78	Line 84	Line 111	Line 163	Line 165	Line 191	Line 339	Line 503	Line 593	Line 666	Line 667
44204	Laparoscopy, surgical; colectomy, partial, with anastomosis	X	X	<del>X</del>	X	<del>X</del>	<del>X</del>	X	X	<del>X</del>	<del>X</del>			X
44205	with removal of terminal ileum with ileocolostomy	X	X	<del>X</del>	X	<del>X</del>	<del>X</del>	X	X	<del>X</del>	<del>X</del>		<del>X</del>	<del>X</del>
44206	with end colostomy and closure of distal segment (Hartmann type procedure)	X	X	X	X	X	X	X	X	X	X			X
44207	with anastomosis, with coloproctostomy (low pelvic anastomosis)	X	X	X	X	X	X	X	X	X	X			X
44208	with anastomosis, with coloproctostomy (low pelvic anastomosis) with colostomy	X	X	X	X	X	X	X	X	X	X			X
44213	Laparoscopy, surgical, mobilization (take-down) of splenic flexure performed in conjunction with partial colectomy (List separately in addition to primary procedure)	X	X	X	X	X	X	X	X	X	X	<del>X</del>		<del>X</del>

Line 35 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE

Line 48 INTUSSUCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, AND FOREIGN BODY IN STOMACH, INTESTINES, COLON, AND RECTUM

Line 78 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS

Line 84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION

Line 111 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

Line 163 ACUTE VASCULAR INSUFFICIENCY OF INTESTINE

Line 165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS

Line 191 DIVERTICULITIS OF COLON

Line 339 CANCER OF ESOPHAGUS

Line 503 RECTAL PROLAPSE

Line 666 BENIGN POLYPS OF VOCAL CORDS

Line 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM

## **DRAFT Scoring Criteria for the HSC Individual and Population Health Impact Measures**

### Impact of Condition on Health without Treatment

- 0 – No impact on health (beyond the short term)
- 1 – Nonfatal condition with a marginal impact on health and/or functional status
- 2 – Nonfatal condition with a modest impact on health and/or functional status
- 3 – Nonfatal condition with a low probability of a significant residual effect or a high probability of a residual effect with a moderate impact on health and/or functional status
- 4 – Nonfatal condition with a low probability (<20%) of significant disability
- 5 – Nonfatal condition with at least a moderate probability ( $\geq 20\%$ ) of significant disability or has a low fatality rate (<10%) and condition is not likely to shorten lifespan by more than 10 years
- 6 – Moderately fatal condition (10-30%) and condition is not likely to shorten lifespan by more than 10 years, or has a low fatality rate and lifespan likely reduced by 10 to 35 years
- 7 – Highly fatal condition (>30%) and condition is not likely to shorten lifespan by more than 10 years; moderately fatal with lifespan likely reduced by 10 to 35 years; or has a low fatality with lifespan likely reduced by 35 to 60 years
- 8 – Highly fatal condition with lifespan likely reduced by 10 to 35 years; moderately fatal with lifespan likely reduced by 35 to 60 years; or has a low fatality rate and lifespan likely to be shortened by 60 years or more
- 9 – Highly fatal condition with lifespan likely reduced by 35 to 60 years or moderately fatal and lifespan likely to be shortened by 60 years or more
- 10 – Highly fatal condition and lifespan likely to be shortened by 60 years or more

### Impact on Pain and Suffering

- 0 – No impact on pain or suffering
- 1 – Intermittent pain of moderate level or frequent pain of low level and/or low level of suffering of the individual, immediate family or caregiver
- 2 – Frequent pain of moderate level or constant pain of low level and/or modest level of suffering of the individual, immediate family or caregiver
- 3 – Intermittent pain of high level or constant pain of moderate level and/or moderate level of suffering of the individual, immediate family or caregiver
- 4 – Frequent pain of high level and/or high level of suffering of the individual, immediate family or caregiver
- 5 – Constant pain of high level and/or extreme suffering of the individual, immediate family or caregiver

### Population Effects

- 0 – No impact on population health
- 1 – Nontreatment would result in limited spread of a significant nonfatal disease or have a low impact on population safety (e.g. due to the nontreatment of a mental health condition)
- 2 – Nontreatment would result in a moderate spread of a significant nonfatal disease or have a modest impact on population safety
- 3 – Nontreatment would result in a limited spread of a potentially fatal disease or a wide spread of a significant nonfatal disease or have a moderate impact on population safety

- 4 – Nontreatment would result in a moderate spread of a potentially fatal disease or have a high impact on population safety
- 5 – Nontreatment would result in a wide spread of a potentially fatal disease or have a very high impact on population safety

#### Impact on Vulnerable Populations

- 0 – No impact on vulnerable populations
- 1 – Somewhat disproportionate impact of a condition with a moderate impact on health on one or more vulnerable populations (does not include men, women, children or pregnant women considered as separate populations or low-income individuals, since methodology is only being applied to Medicaid population at this point)
- 2 – Moderately disproportionate impact of a condition with a moderate impact on health on one or more vulnerable populations
- 3 – Somewhat disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations
- 4 – Moderately disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations
- 5 – Highly disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations

#### Tertiary Prevention

- 0 – No tertiary prevention provided by treatment and early treatment does not prevent progression of the disease
- 1 – Treatment will prevent of moderate complication and/or early treatment may prevent progression of the disease resulting in a moderate impact on health
- 2 – Low to modest likelihood that treatment will prevent a significant complication or prevent progression of the disease resulting in significant impact on health
- 3 – Moderate to high likelihood that treatment will prevent a significant complication or prevent progression of the disease resulting in significant impact on health
- 4 – Low to modest likelihood that treatment will prevent severely debilitating complication and/or early treatment with prevent progression of disease leading to severe disability or death
- 5 – Moderately to high likelihood that treatment will prevent severely debilitating complication and/or early treatment with prevent progression of disease leading to severe disability or death

#### Effectiveness

- 0 – No demonstrated effectiveness (<5%) or causes harm
- 1 - Achieves desired result in 5-25% of cases
- 2 - Achieves desired result in 25-50% of cases
- 3 – Achieves desired result in 50-75% of cases
- 4 – Achieves desired result in 75-95% of cases
- 5 – Achieves desired result in 95+% of cases

#### Net Cost

- 0 – Very high cost (>\$100,000)
- 1 – High cost (\$20,000-\$100,000)
- 2 – Moderate cost (\$5,000-\$20,000) or higher cost somewhat offset by cost of treatment alternative

- 3 – Modest cost (\$1,000-\$5,000) or higher cost significantly offset by cost of treatment alternative
- 4 – Low cost (<\$1,000) or higher cost nearly offset by cost of treatment alternative
- 5 – Cost savings

## **Section 7**

### **Methodology**

## Population and Individual Impact Measures

**Impact on Health Life Years** - to what degree will the condition impact the health of the individual if left untreated, considering the median age of onset (i.e., does the condition affect mainly children, where the impacts could potentially be experienced over a person's entire lifespan)? Range of 0 (no impact) to 10 (high impact).

**Impact on Suffering** - to what degree does the condition result in pain and suffering? Effect on family members (e.g. dealing with a loved one with Alzheimer's disease or needing to care for a person with a life-long disability) should also be factored in here. Range of 0 (no impact) to 5 (high impact).

**Population Effects** - the degree to which individuals other than the person with the illness will be affected. Examples include public health concerns due the spread of untreated tuberculosis or public safety concerns resulting from untreated severe mental illness. Range of 0 (no effects) to 5 (widespread effects).

**Vulnerability of Population Affected** - to what degree does the condition affect vulnerable populations such as those of certain racial/ethnic decent or those afflicted by certain debilitating illnesses such as HIV disease or alcohol & drug dependence? Range of 0 (no vulnerability) to 5 (high vulnerability).

**Tertiary Prevention** - in considering the ranking of services within new categories 6 and 7, to what degree does early treatment prevent complications of the disease (not including death)? Range of 0 (doesn't prevent complications) to 5 (prevents severe complications).

**Effectiveness** - to what degree does the treatment achieve its intended purpose? Range of 0 (no effectiveness) to 5 (high effectiveness).

<b>Healthy Life Years Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Sexual Dysfunction	Anogenital Viral Warts	Tourette's Disorder And Tic Disorders	Termination Of Pregnancy	Pituitary Dwarfism	Chronic Organic Mental Disorders Including Dementias
Disorders Of Sleep Without Sleep Apnea	Anti-Social Personality Disorder	Dental Conditions (Eg. Periodontal Disease)	Incontinence Of Feces	Schizotypal Personality Disorders	Autism Spectrum Disorders
<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	
Abuse Or Dependence Of Psychoactive Substance	Drug Withdrawal Syndrome In Newborn	HIV Disease And Related Opportunistic Infections	Cystic Fibrosis	Very Low Birth Weight (Under 1500 Grams)	
Tobacco Dependence	Tuberculosis	Life-Threatening Cardiac Arrhythmias	Acute And Subacute Necrosis Of Liver; Specified Inborn Errors Of Metabolism (Eg. Maple Syrup Urine Disease, Tyrosinemia)	Short Bowel Syndrome - Age 5 Or Under	

<b>Pain And Suffering Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Anogenital Viral Warts	Anti-Social Personality Disorder	Sexual Dysfunction	Tourette's Disorder And Tic Disorders	Autism Spectrum Disorders	Chronic Organic Mental Disorders Including Dementias
Acute Viral Conjunctivitis	Pituitary Dwarfism	Disorders Of Sleep Without Sleep Apnea	Abuse Or Dependence Of Psychoactive Substance	Cystic Fibrosis	Very Low Birth Weight (Under 1500 Grams)
Chronic Bronchitis	Schizotypal Personality Disorders	Termination Of Pregnancy		Short Bowel Syndrome - Age 5 Or Under	

<b>Population Effects Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Sexual Dysfunction	Life-Threatening Cardiac Arrhythmias	Anogenital Viral Warts	HIV Disease And Related Opportunistic Infections	Anti-Social Personality Disorder	Chronic Hepatitis; Viral Hepatitis
Disorders Of Sleep Without Sleep Apnea	Autism Spectrum Disorders	Tobacco Dependence	Termination Of Pregnancy	Tuberculosis	Abuse Or Dependence Of Psychoactive Substance

<b>Vulnerability Of Population Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Pituitary Dwarfism	Very Low Birth Weight (Under 1500 Grams)	Tourette's Disorder And Tic Disorders	Drug Withdrawal Syndrome In Newborn	Chronic Hepatitis; Viral Hepatitis	HIV Disease And Related Opportunistic Infections
Cystic Fibrosis	Tobacco Dependence	Anogenital Viral Warts	Incontinence Of Feces	Tuberculosis	

<b>Effectiveness Of Treatment Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Acute Viral Conjunctivitis	Schizotypal Personality Disorders	Tobacco Dependence	Life-Threatening Cardiac Arrhythmias	Cystic Fibrosis	Pituitary Dwarfism
Chronic Bronchitis	Anti-Social Personality Disorder	Tourette's Disorder And Tic Disorders	Sexual Dysfunction	HIV Disease And Related Opportunistic Infections	Termination Of Pregnancy

<b>Tertiary Prevention Score Examples</b>					
<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
Cancer Of Pancreas	Stroke	Urinary Incontinence	Iron Deficiency Anemia And Other Nutritional Deficiencies	Diabetes Mellitus With End Stage Renal Disease	Acute And Subacute Ischemic Heart Disease, Myocardial Infarction
Ruptured Spleen	Sexual Dysfunction	Cleft Palate And/Or Cleft Lip	Chronic Hepatitis; Viral Hepatitis	Injury To Internal Organs	Acute Stress Disorder
Minor Burns	Acute Bronchitis And Bronchiolitis	Depression And Other Mood Disorders, Mild Or Moderate	Superficial Injuries With Infection	Ulcers, Gastritis, Duodenitis, And Gi Hemorrhage	Hearing Loss - Age 5 Or Under