

## Bisphosphonate Step Therapy Criteria

Program may be implemented with the following options:

- 1) Option 1: generic before brand bisphosphonate OR
- 2) Option 2: generic before preferred brand before nonpreferred brand bisphosphonate

For Blue Cross and Blue Shield of Illinois Option 1 (1-step step therapy) will apply.

Boniva Injection will NOT be included in this step therapy program for Blue Cross and Blue Shield of Illinois because these plans do not cover injectable bisphosphonates under the pharmacy benefit.

Brand	Generic	Dosage Form
Actonel <sup>®</sup>	risedronate	oral tablets
Actonel <sup>®</sup> with Calcium	risedronate/calcium carbonate	oral tablets
Boniva <sup>®</sup>	ibandronate	oral tablets, injection
Fosamax <sup>®</sup>	alendronate	oral tablets <sup>a</sup> , oral solution
Fosamax Plus D <sup>®</sup>	alendronate/cholecalciferol	oral tablets

<sup>a</sup> generic available

### PROGRAM OBJECTIVES

The intent of the step therapy criteria for the bisphosphonate agents is to encourage the use of cost-effective generic alendronate before more expensive brand bisphosphonate agents (Option 1) **or** generic alendronate and preferred brand(s) over the more expensive nonpreferred brand bisphosphonate agents (Option 2) and to accommodate for use of brand agents when generic alendronate (Option 1) or generic alendronate and preferred brands (Option 2) cannot be used due to previous trial and failure, allergy, intolerance, or contraindication. The edit also allows automatic payment of claims for a brand bisphosphonate when a patient is already stabilized on the agent. Requests for brand bisphosphonates not meeting the electronic edit requirements will be reviewed through the manual review process.

### PROGRAM FUNCTIONALITY

#### Electronic Edits

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit. If the patient has not met the requirements, the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

The bisphosphonate step therapy program may be implemented as one of two step therapy options:

- Option 1: a 1-step edit that requires therapy with a generic bisphosphonate agent within 90 days prior to a brand claim
- Option 2: a 2-step edit that requires prior use of a generic bisphosphonate agent within 90 days prior to payment for a preferred brand and use of both a generic and a preferred brand bisphosphonate agent within 180 days prior to a nonpreferred brand claim.

**Table 1: Summary of Bisphosphonates 1-Step Option**

Targeted Agent(s)	Actonel, Actonel with Calcium, Boniva, Fosamax, Fosamax Plus D
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days <sup>a</sup> )
Prerequisite Agent(s)	generic alendronate
Number of prerequisites required	1
Prerequisite look-back time frame	90 days <sup>a</sup>
Age-related edit?	NA
Additional Comments	The injectable (IV) dosage form of Boniva is not included in this step therapy program.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

**Table 2: Details of Bisphosphonates 1-Step Option**

Targeted Agents	GPIs (multisource code)	Prior Agents	GPIs (multisource code)	Look-back Time frames
<b>ANY ONE of:</b> Actonel Actonel with Calcium Boniva Fosamax Fosamax Plus D	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O)	<b>For Prerequisites, ANY ONE of:</b> generic alendronate	3004201010**** (Y)	<b>Prerequisite look-back time frame</b>  90 days <sup>a</sup>
		<b>For auto-grandfathering, ANY ONE of:</b> Actonel Actonel with Calcium Boniva Fosamax Fosamax Plus D	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>Auto-grandfathering look-back time frame:</b>  90 days <sup>a</sup>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

**Table 3: Summary of Bisphosphonates 2-Step Option**

	Preferred Brand	Nonpreferred Brand
Targeted Agent(s)	All preferred brand bisphosphonates, determined by client	All nonpreferred brand bisphosphonate products, determined by client
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days <sup>a</sup> )	Yes (90 days <sup>a</sup> )
Prerequisite Agent(s)	generic alendronate	generic alendronate AND a preferred brand bisphosphonate
Number of prerequisites – bisphosphonate agents	1	2
Prerequisite look-back time frame for Bisphosphonate prerequisites	90 days <sup>a</sup>	180 days <sup>b</sup>
Age-related edit?	NA	NA
Additional Comments	The injectable (IV) dosage form of Boniva is not included in this step therapy program.	

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 180 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 180 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 270 days.

**Table 4: Details of Bisphosphonates 2-Step Option**

Targeted Agents	GPIs (multisource code)	Prior Agents	GPIs (multisource code)	Look-back Time frames
Preferred brand bisphosphonate agents, determined by client	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>For Prerequisites, ANY ONE of:</b> generic alendronate	3004201010**** (Y)	<b>Prerequisite look-back time frame:</b>  90 days <sup>a</sup>
		<b>For auto-grandfathering, ANY ONE of:</b> Actonel Actonel with Calcium Boniva Fosamax Fosamax Plus D	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>Auto-grandfathering look-back time frame:</b>  90 days <sup>a</sup>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

**Table 4: Details of Bisphosphonates 2-Step Option (cont.)**

Targeted Agents	GPIs (multisource code)	Prior Agents	GPIs (multisource code)	Look-back Time frames
Nonpreferred brand, determined by client	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>For Prerequisites, ANY ONE of:</b> generic alendronate  <b>AND</b> <b>ANY ONE of:</b> Preferred brand bisphosphonate agent, determined by client	3004201010**** (Y)  AND Determined by client- 3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>Prerequisite look-back time frame:</b>  180 days <sup>b</sup>
		<b>For auto-grandfathering, ANY ONE of:</b> Actonel Actonel with Calcium Boniva Fosamax Fosamax Plus D	3004206510**** 3004206511**** 3004204810**** 3004201010**** 3004201020**** (M, N, or O) set up at drug or GPI 10 level	<b>Auto-grandfathering look-back time frame:</b>  90 days <sup>a</sup>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 365 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 395 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 455 days (assuming claims history data extends back this far).

**Prior Authorization (PA) Criteria for Approval**

The Prior Authorization (PA) Criteria for Approval provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are consistent with those set up in the electronic edit. The intent of the PA Criteria for Approval for the bisphosphonate agents is to ensure that patients who have been unable to tolerate the required prerequisite bisphosphonate(s) or have not had adequate response to one of these agents have the option of treatment with the requested brand agent. Approval will be given to patients who have a history of trial and failure of generic alendronate (Option 1) or generic alendronate and a preferred bisphosphonate agent (Option 2) outside of the 90-day look-back period (Option 1) or outside the 180-day look-back period (Option 2) or outside of the current benefit plan. The requested brand agent may also be approved if the patient has tried generic alendronate (Option 1) or generic alendronate and a preferred brand (Option 2) and discontinued due to allergy, intolerance, or contraindication to the agent, if the patient is currently receiving and stabilized on the brand agent, or if the physician has submitted documentation to support the use of the requested brand agent for the patient.

**Step Therapy PA Criteria for Approval**  
***Bisphosphonate Step Therapy Option 1***  
**Initial and Renewal Evaluation**

1. Has the Bisphosphonate Step Therapy criteria been implemented with a 1-step option (Option 1)?  
If yes, continue to 2. If no, go to appropriate criteria question set.
2. Is the patient currently being treated with the requested brand bisphosphonate?  
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient's medication history indicate previous use of the generic bisphosphonate alendronate?  
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, contraindication, or intolerance to generic alendronate?  
If yes, approve for 12 months. If no, deny.

***Bisphosphonate Step Therapy Option 2***  
**Initial and Renewal Evaluation**

1. Has the Bisphosphonate Step Therapy criteria been implemented with a 2-step option (Option 2)?  
If yes, continue to 2. If no, go to appropriate criteria question set.
2. Is the patient currently being treated with the requested brand bisphosphonate?  
If yes, approve for 12 months. If no, continue to 3.
3. What drug is requested?
  - a. generic bisphosphonate
  - b. preferred brand bisphosphonate
  - c. nonpreferred brand bisphosphonateIf a, review is not applicable. Claim will adjudicate. If b, continue to 4. If c, continue to 6.
4. Has the patient tried and failed the generic bisphosphonate alendronate?  
If yes, approve requested preferred brand for 12 months. If no, continue to 5.
5. Does the patient have an allergy, contraindication, or intolerance to the generic bisphosphonate alendronate?  
If yes, approve requested preferred brand for 12 months. If no, deny.
6. Has the patient tried and failed the generic bisphosphonate alendronate?  
If yes, continue to 8. If no, continue to 7.
7. Does the patient have an allergy, contraindication, or intolerance to the generic bisphosphonate alendronate?  
If yes, continue to 8. If no, deny.
8. Has the patient tried and failed a preferred brand bisphosphonate?  
If yes, approve requested nonpreferred brand agent for 12 months. If no, continue to 9.
9. Does the patient have an allergy, contraindication, or intolerance to a preferred brand bisphosphonate?  
If yes, approve requested nonpreferred brand agent for 12 months. If no, deny.

**CLINICAL RATIONALE**

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures. An estimated 10 million people in the United States are affected, 80% of which are women.<sup>1</sup> The major consequence of osteoporosis is fracture, up to 1.5 million per year attributed to the disease. These fractures can lead to diminished physical functioning, reduction in quality of life, and increased mortality.<sup>2</sup>

Treatment of Osteoporosis includes reduction of modifiable risk factors for fracture, increasing calcium and vitamin D intake, stimulating bone formation through increased activity, and reducing risk of falls.<sup>3-5</sup> Pharmacologic intervention should be considered for patients at high risk of fractures.<sup>3-5</sup> Treatments include antiresorptive agents (estrogen with or without progestin, the selective estrogen receptor modulator raloxifene, bisphosphonates, and calcitonin) or the anabolic agent, teriparatide. The nitrogen-containing bisphosphonates have been a major choice for therapy for post-menopausal osteoporosis, osteoporosis in men, and glucocorticoid-induced osteoporosis.<sup>3-5</sup>

Guidelines for the treatment of osteoporosis recommend a bisphosphonate agent as first-line treatment for both primary and secondary prevention of fractures (see Formulary Chapter 4.9A /Calcium Regulators/Osteoporosis Agents).<sup>6</sup> Alendronate and risedronate are both consistently mentioned as appropriate choices for initial treatment.<sup>4-6</sup>

Outcome studies evaluating the efficacy alendronate and risedronate in post-menopausal women have been published.<sup>6,7</sup> A summary of the outcomes for alendronate and risedronate are provided in Table 5. Data in this table was published before the approval of ibandronate.

**Table 5. Fracture Outcomes<sup>6,7</sup>**

<b>Condition</b>	<b>Risedronate (Actonel)</b>	<b>Alendronate (Fosamax)</b>
Primary Prevention of Vertebral Fractures	<b>No</b>	<b>Yes</b> (ARR 1.7%)
Secondary Prevention of Vertebral Fractures	<b>Yes</b> (ARR 5%-7.4%)	<b>Yes</b> (ARR 8.0%)
Primary Prevention of Hip Fractures	<b>No</b>	<b>No</b>
Secondary Prevention of Hip Fractures	<b>Yes</b> (ARR 1.4%)	<b>Yes</b> (ARR 1.1%)
Prevention of Glucocorticoid Induced Vertebral Fractures	<b>Yes</b> (ARR 11%)	<b>Yes</b> (ARR 6.1%)

ARR=absolute risk reduction

Approval of ibandronate for the treatment of osteoporosis by the Food and Drug Administration (FDA) was based on a three-year phase III trial (BONE).<sup>8</sup> Data from the BONE study demonstrated that daily ibandronate, relative to placebo, significantly reduced the 3-year risk for vertebral fracture from 9.6% to 4.7% (p=0.0001).<sup>8</sup> Approval for the prevention of osteoporosis was based on a two-year trial.<sup>8</sup> Data from the osteoporosis prevention study submitted to the FDA demonstrated ibandronate 2.5 mg relative to placebo, increased BMD of the lumbar spine and hip by 3.0% and 2.0% respectively.<sup>9</sup> Data from the MOBILE study, submitted to the FDA for approval of once-monthly dosing, demonstrated that monthly ibandronate had at least an equal increase in BMD of the lumbar spine and hip compared to the daily administration of ibandronate.<sup>10</sup> Women treated with the 150 mg/month dose compared to Boniva 2.5 mg daily had the greatest increase in BMD.<sup>10</sup>

## FDA APPROVED INDICATIONS

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization (PA) Criteria for Approval."

**Table 6: FDA Approved Indications<sup>11-16</sup>**

Available Products	FDA Indications <sup>11-16</sup>					
	Prevention of Osteoporosis in Post-menopausal women	Treatment of Osteoporosis Post-menopausal women	Treatment to Increase Bone Mass in Men with Osteoporosis	Treatment of Paget's Disease	Prevention of Glucocorticoid Induced Osteoporosis	Treatment of Glucocorticoid Induced Osteoporosis
Actonel (risedronate tablets)	✓	✓	✓	✓	✓	✓
Actonel with Calcium (risedronate tablets/calcium carbonate tablets)	✓	✓				
Boniva (ibandronate tablets)	✓	✓				
Boniva (ibandronate injection)		✓				
Fosamax (alendronate tablets, solution)	✓	✓	✓	✓		✓
Fosamax Plus D (alendronate/cholecalciferol tablets)		✓	✓			

1U=International Units, mg=milligrams, mL=milliliters

<sup>a</sup> generic available

## REFERENCES

1. National Osteoporosis Foundation. Fast facts on osteoporosis. Available at; <http://www.nof.org/osteoporosis/diseasefacts.htm>. Accessed November 9, 2009.
2. US Department of Health and Human Services. Bone Health and Osteoporosis: a Report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004.
3. Institute for Clinical Systems Improvement. Health Care Guideline: Diagnosis and Treatment of Osteoporosis. Sixth Edition 2008. Available at: [http://www.icsi.org/guidelines\\_and\\_more/gl\\_os\\_prot/womens\\_health/osteoporosis/osteoporosis\\_diagnosis\\_and\\_treatment\\_of\\_.html](http://www.icsi.org/guidelines_and_more/gl_os_prot/womens_health/osteoporosis/osteoporosis_diagnosis_and_treatment_of_.html). Accessed November 9, 2009.
4. NICE technology appraisal guidance 160. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Available at <http://guidance.nice.org.uk/TA160/Guidance/pdf/English>. Accessed on October 28, 2009.
5. NICE-Technology Appraisal 161: Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. October 2008. Available at. <http://www.nice.org.uk/nicemedia/pdf/TA161guidanceword.pdf>. Accessed on October 29, 2009.
6. Prime Therapeutics Formulary Chapter 4.9A Calcium Regulators/Osteoporosis Agents. July 2009.
7. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Review 2008 Jan 23(1):CD004523.

8. Cooper C, Emkey RD, McDonald, et al. Oral ibandronate osteoporosis vertebral fracture trial in North America and Europe (BONE). [Study #4411 in FDA Medical Review]. FDA Medical Review Application #21-455 Boniva Oct 2003. Accessed 06/27/05 @ [http://www.fda.gov/cder/foi/nda/2003/21-455\\_Boniva\\_medr\\_P1.pdf](http://www.fda.gov/cder/foi/nda/2003/21-455_Boniva_medr_P1.pdf) also published in *J Bone Miner Res* 2004;19(8):1241-1249.
9. McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early menopausal women without osteoporosis. *J Bone Miner Res* 2004;19:11-18.
10. Miller PD, McClung, Macovei L, et al. Monthly oral ibandronate therapy in post-menopausal osteoporosis: 1 year results from the MOBILE study. *J Bone Miner Res* 2005;20(8):1315-1322.
11. Actonel prescribing information. Sanofi-Aventis U.S. LLC/Proctor & Gamble Pharmaceuticals, Inc. April 2008.
12. Actonel with Calcium prescribing information. Sanofi-Aventis U.S. LLC/Proctor & Gamble Pharmaceuticals, Inc. February 2008.
13. Boniva prescribing information. Roche Laboratories, Inc. November 2008.
14. Boniva Injection prescribing information. Roche Laboratories, Inc. February 2007.
15. Fosamax prescribing information. Merck & Co., Inc. February 2008.
16. Fosamax Plus D prescribing information. Merck & Co., Inc. February 2008.

**Document History**

Criteria developed from PS\_Fosamax\_ST/QL\_0208 and PS\_Bisphosphonate\_QL\_AR1107 approved by P & T UM Committee 08/2008

Criteria changed to bisphosphonate step therapy, approved by P & T UM Committee 02/2009

Initial Client Review, Client Specific Criteria, approved by HCSC Corporate Clinical Committee, 08/2009

Administrative Addition, revision to textbox to indicate Boniva injection is not included in program 09/2009

Annual Review, Prime Standard Criteria approved by P & T UM Committee 02/2010

Client Annual Review, Prime Standard criteria approved by HCSC Corporate Clinical Committee 03/2010