

Horizon BCBSNJ
 Medical Necessity and Appropriateness Guideline

Section
Policy Number
Effective Date 6/25/04
Review Date 7/22/05

Subject:

COX 2 INHIBITORS

BRAND NAME: **Celebrex***
(Generic) **(celecoxib)**

Vioxx (Withdrawn from the market 09-2004)
(rofecoxib)

Bextra (Withdrawn from the market 02-2005)
(valdecoxib)

Mobic
(meloxicam)

* Celebrex 400 mg excluded from the step therapy protocol, but is included in the post-step therapy review criteria.

FDA-APPROVED INDICATIONS

Celebrex is indicated:

1. For the relief of the signs and symptoms of osteoarthritis
2. For the relief of the signs and symptoms of rheumatoid arthritis in adults
3. For the relief of signs and symptoms of ankylosing spondylitis.
4. For the management of acute pain in adults
5. For the treatment of primary dysmenorrhea
5. To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celebrex treatment will persist after Celebrex is discontinued. The efficacy and safety of Celebrex treatment in patients with FAP beyond six months have not been studied.

Mobic is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Mobic is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older.

INITIAL STEP THERAPY PROTOCOL CRITERIA

The patient must meet at least one of the following requirements under a Horizon prescription benefit in the previous 4 months:

- filled at least one pharmacological indicator of a risk factor for developing GI adverse events (Table 2) filled for at least a 30-day supply

Then, the drug will process for up to the maximum FDA approved dosing to ensure appropriate use and to minimize adverse events.

Table 1

| DRUG | STRENGTH | DISPENSING LIMIT |
|-------------|-----------------|-------------------------|
| Celebrex | 100 mg | 60 capsules per 25 days |

| | | |
|----------|--------------|-------------------------|
| Celebrex | 200 mg | 60 capsules per 25 days |
| Mobic | 7.5 mg | 30 tablets per 25 days |
| Mobic | 15 mg | 30 tablets per 25 days |
| Mobic | 7.5 mg/ 5 ml | 300 ml per 25 days |

* The duration of 25 days is used for a 30 day fill period to allow time for refill processing. If a mail order option is available, a quantity of 3 x 25 day quantity per 75 days is used for a 90 day fill period to allow time for refill processing.

Note: Celebrex 400 mg capsules will be provided for the diagnosis of FAP through the post-step therapy review process only.

Table 2

| |
|---|
| Pharmacological Indicators for a Risk of GI Adverse Events |
| Anticoagulant Therapy |
| Oral Corticosteroid Therapy |

POST STEP THERAPY REVIEW CRITERIA

CELEBREX

| | | |
|---|-----|----|
| 1. Is the patient 18 years old or older? | Yes | No |
| 2. Does the patient have the diagnosis of adenomatous colorectal polyps in familial adenomatous polyposis (FAP)? [Tech Only: If the answer to this question is no, then may skip to question 4.] | Yes | No |
| 3. Is the patient aware that Celebrex should be added to his/her current treatments for colorectal polyps? (Celebrex should not replace current treatments.) [Tech Only: Skip to question 5.] | Yes | No |
| 4. Is the patient at risk for a severe NSAID-induced GI adverse event? (Risk factors may include: history of peptic ulcer or GI bleed, or concomitant use of corticosteroids or anticoagulants.) | Yes | No |
| 5. Is the prescription for Celebrex 400 mg capsules? | Yes | No |
| 6. Has the patient experienced severe allergic-type reactions after taking aspirin or another NSAID? | Yes | No |
| 7. Has the patient experienced severe allergic-type reactions after taking sulfonamides? | Yes | No |
| 8. Has the physician evaluated the cardiovascular risks for the patient? | Yes | No |
| 9. Is the patient being treated for post-operative pain following CABG surgery? | Yes | No |
| 10. Does this request exceed the maximum FDA-approved dosing? | Yes | No |

If the member meets the criteria based on the following table listed below, the medication will be approved for 12 months.

Guidelines for Appropriateness

| Duration of Appropriateness | | 12 Months | |
|-----------------------------|--|-------------------------|---|
| Appropriate Quantities | For Diagnosis of FAP ONLY #60 capsules of 400 mg /25 days | For All Other Diagnoses | #60 capsules of 100 mg or 200 mg /25 days |
| Set 1 | | Set 2 | |
| Yes to question(s) | No to question(s) | Yes to question(s) | No to question(s) |
| 1 | 6 | 1 | 2 |

| | | | |
|---|----|---|----|
| 2 | 7 | 4 | 5 |
| 3 | 9 | 8 | 6 |
| 5 | 10 | | 7 |
| 8 | | | 9 |
| | | | 10 |

Note: Mail order quantities will be three times the 25 day quantities per 75 days.

POST STEP THERAPY REVIEW CRITERIA:

MOBIC

- | | | |
|--|-----|----|
| 1. Is the patient 2 years old or older? | Yes | No |
| 2. Is the patient at risk for NSAID-induced GI adverse events? (Risk factors may include, but are not limited to, the following: age 60 years or older; history of peptic ulcer or GI bleed; concomitant use of corticosteroids or anticoagulants; or high dose NSAID use.) | Yes | No |
| 3. Has the patient experienced a severe allergic-type reaction after taking aspirin, or another NSAID? (e.g., asthma, urticaria, or anaphylaxis) | Yes | No |
| 4. Has the physician evaluated the cardiovascular risks for the patient? | Yes | No |
| 5. Is the patient being treated for post-operative pain following CABG surgery? | Yes | No |
| 6. Does this request exceed the maximum FDA-approved dosing? | Yes | No |

If the member meets the criteria based on the following table listed below, the medication will be approved for 12 months.

| Guidelines for Appropriateness | |
|---------------------------------------|--|
| Appropriate Duration | 12 months |
| Appropriate Quantities | For 7.5 or 15 mg #30 tablets per 25 days For 7.5 mg/5 ml 300 ml per 25 days |
| Set 1 | |
| Yes to question(s) | No to question(s) |
| 1 | 3 |
| 2 | 5 |
| 4 | 6 |

Note: Mail order quantities will be three times the 25 day quantities per 75 days.

* The duration of 25 days is used for a 30 day fill period to allow time for refill processing. The duration of 75 days is used for a 90 day fill period to allow time for refill processing.

BLACK BOX WARNING

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- Celebrex/Mobic is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs, including Celebrex, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

RATIONALE

Step Therapy Protocol

The pre-requisite therapy is based on the risk factors for NSAID-associated adverse GI events,^{1,4,5,6,7} There is no evidence to support the use of more expensive preparations over cheaper ones or the use of the modified release preparations.² Clinical trials suggest that COX 2 inhibitors may produce a lower incidence of GI adverse events.^{1,3} If the patient has had pharmacological therapy that demonstrates a risk for adverse GI events, then no authorization is necessary. The patient must have tried and failed two traditional NSAIDs after a two week trial of each. A two week trial should be given before any NSAID therapy is stopped for lack of efficacy.^{5,7} A 30-day trial of anticoagulant therapy or oral corticosteroid therapy is to demonstrate that the patient is taking these drugs on a daily basis, since short term therapy does not put patient at long term risk for an NSAID-induced GI adverse event. The four month review period was selected to ensure current use, yet allow for patients utilizing mail services.. Once the steps are met, a limit is placed on the quantity of drug that will process. These limits will allow up to the maximum recommended dosage for the drug. If the pre-requisite therapy does not provide evidence of a risk factor, then patient must meet the clinical *post step therapy review criteria for Approval*. Celebrex 400 mg will not be included in the step therapy, as this dosage is appropriate for patients with a diagnosis of familial adenomatous polyposis (FAP) only. The 400 mg capsules will be available through the *post step therapy review* process.

Post step therapy review Criteria

If the patient has the diagnosis of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), then the patient must be informed that the usual care of FAP should not be altered because of the concurrent administration of Celebrex.¹ If the patient does not have the diagnosis of FAP, the patient must have tried and failed two traditional NSAIDs after a two week trial of each. A two week trial should be given before any NSAID therapy is stopped for lack of efficacy.^{5,7} Clinical trials suggest that COX 2 inhibitors may have produce a lower incidence of GI adverse events.^{1,3} Future studies are necessary to assess long term risk. If the Step Therapy edit does not find a previous paid claim for a 14-day supply of NSAID therapy or a pharmacological indicator of a risk factor for developing GI adverse events, questions addressing previous therapy are repeated to ensure that all previous trials are taken into account. Per the FDA approved product labeling, NSAIDs and COX-2s should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking sulfonamides (for Celebrex or Bextra), aspirin or other NSAIDs.^{1,4} Approval will be given for quantities up to the maximum recommended dose.

Mobic will be included in this document. Mobic does not offer advantages over traditional NSAIDS, but may be used as an alternative.

ADDITIONAL INFORMATION^{1,4}

CELEBREX

Osteoarthritis:

The dose recommended for the relief of the signs and symptoms of osteoarthritis is 200 mg administered as a single dose or 100 mg twice per day.

Rheumatoid Arthritis:

The dose recommended for the relief of the signs and symptoms of rheumatoid arthritis are 100 to 200 mg twice per day.

Management of Acute Pain and the Treatment of Primary Dysmenorrhea:

The recommended dose is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice per day as needed.

Familial Adenomatous Polyposis (FAP):

Usual medical care for FAP patients should be continued while on Celebrex. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended dose is 400 mg twice per day to be taken with food.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be sought for the shortest possible duration for each patient. Possible risk factors for NSAID-induced adverse GI complications include: age 60 years or

older; history of peptic ulcer or GI bleed; concomitant use of corticosteroids or anticoagulants; or use of consistently high NSAID doses.

Safety and efficacy in pediatric patients below the age of 18 years have not been evaluated.

Familial adenomatous polyposis (FAP): Treatment with Celebrex in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patient should not be altered because of the concurrent administration of Celebrex. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed. |

Because of its lack of platelet effects, Celebrex is not a substitute for aspirin for cardiovascular prophylaxis.

MOBIC

Mobic is an oxycam derivative. Mobic is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action, **like that of other NSAIDs** may be related to prostaglandin synthetase (cyclooxygenase) inhibitor. **As with other NSAIDs**, higher doses of Mobic were associated with an increased risk of serious GI events, therefore the daily dose of Mobic should not exceed 15 mg. The lowest dose of Mobic should be sought for each patient.

Osteoarthritis and Rheumatoid arthritis: The recommended starting and maintenance dosage for the treatment of osteoarthritis is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily. The **MAXIMUM** recommended daily dose of Mobic is 15 mg regardless of the formulation. Mobic oral suspension 7.5 mg/5 mg or 15 mg/10 ml may be substituted for Mobic tablets 7.5 mg or 15 mg, respectively.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Celebrex

Contraindications:

- Celebrex should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.
- COX-2 inhibitors should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs are possible in such patients

Warnings:

- Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and can occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and symptoms of serious GI toxicity and the steps to take if they occur.
- NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies should be used that **DO NOT** involve NSAID therapy (including COX-2 medications).
- Anaphylactoid reactions have occurred in patients without prior exposure to COX-2 drugs. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving COX-2 drugs. COX-2 inhibitors should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.
- For Celebrex cases of hypersensitivity reactions (anaphylactic reactions and angioedema) have been reported in patients receiving COX-2 inhibitors. These cases have occurred in patients with and without a history of allergic-type reactions to sulfonamides.
- **Treatment with Celebrex in familial adenomatous polyposis (FAP) has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy, or other FAP-related surgery. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration**

of Celebrex. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

Precautions:

- COX-2 inhibitors cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.
- The pharmacological activity of COX-2 drugs in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.
- Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, COX-2 inhibitors should be discontinued.
- Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Caution should be used when initiating treatment with COX-2 inhibitors in patients with considerable dehydration. It is advisable to rehydrate the patient first, and then start therapy. Caution is also recommended in patients with pre-existing kidney disease.
- Anemia is sometimes seen in patients receiving COX-2 inhibitors. Patients on long-term treatment should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
- Fluid retention and edema have been observed in some patients taking COX-2 inhibitors. Therefore, COX-2 inhibitors should be used with caution in patients with fluid retention, hypertension or heart failure.
- Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, COX-2 inhibitors should not be administered with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.
- A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction. Use of the COX-2 drugs is not recommended in patients with severe hepatic insufficiency.

Drug Interactions

- ACE Inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme Inhibitors.
- Aspirin
Concomitant administration of low-dose aspirin with COX-2 drugs may result in an increased rate of GI ulceration or other complications, compared to use of COX-2 drugs alone.
- Furosemide
Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients.
- Fluconazole
Concomitant administration of fluconazole with Bextra and Celebrex produced a significant increase in the plasma levels of valdecoxib and celecoxib.
- Lithium
Bextra produced significant decreases in lithium serum clearance and renal clearance. Lithium serum concentrations should be monitored closely when initiating or changing therapy with Bextra.
- Phenytoin
Patients already stabilized on Bextra should be closely monitored for loss of symptom control with phenytoin coadministration.
- Warfarin
COX-2 inhibitors caused a statistically significant increase in plasma exposure of warfarin. Anticoagulant therapy should be monitored, particularly during the first few weeks, after initial therapy.

Pregnancy
Category C

Pediatric Use
Safety and effectiveness of Celebrex and Bextra in pediatric patients below the age of 18 years have not been evaluated.

Mobic

Contraindications:

- Mobic is contraindicated in patients with known hypersensitivity to meloxicam.
- Mobic should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Warnings:

- Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation
Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.
- Anaphylactoid Reactions
Anaphylactoid reactions have occurred in patients without known prior exposure to Mobic. Mobic should not be given to patients with the aspirin triad.
- Advanced Renal Disease
In cases with advanced kidney disease, treatment with Mobic is not recommended. If NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable.
- Pregnancy
Mobic should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

Precautions:

- Mobic cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
- The pharmacological activity of Mobic in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.
- Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking Mobic. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs. Patients with signs and/or symptoms suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MOBIC. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Mobic should be discontinued.
- Renal Effects
Caution should be used when initiating treatment with Mobic in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with Mobic. Caution is also recommended in patients with pre-existing kidney disease.
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.
The extent to which metabolites may accumulate in patients with renal failure has not been studied with Mobic. Because some Mobic metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.
- Hematological Effects
Anemia is sometimes seen in patients receiving Mobic. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with Mobic, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
Drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Mobic does not generally affect platelet counts, prothrombin time (PT), or partial

thromboplastin time (PTT). Patients receiving Mobic who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

- Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking Mobic. Therefore, Mobic should be used with caution in patients with fluid retention, hypertension, or heart failure.

- Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Mobic should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Drug Interactions

- ACE inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

- Aspirin

Concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects.

Concomitant administration of low-dose aspirin with Mobic may result in an increased rate of GI ulceration or other complications, compared to use of Mobic alone.

Mobic is not a substitute for aspirin for cardiovascular prophylaxis.

- Furosemide

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with furosemide and Mobic, patients should be observed closely for signs of declining renal function, as well as to assure diuretic efficacy.

- Lithium

Patients on lithium treatment should be closely monitored when Mobic is introduced, adjusted, or withdrawn.

- Warfarin

Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing Mobic therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding.

Pregnancy

Category C

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

Caution should be exercised in treating the elderly (65 years and older).

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