

NEW DRUG UPDATE

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Bextra® (valdecoxib)

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Introduction

Bextra[®] [valdecoxib (val-de-KOX-ib)] is a new selective cyclooxygenase-2 (COX-2) nonsteroidal anti-inflammatory that was approved by the FDA in November 2001. It displays anti-inflammatory, analgesic, and antipyretic effects by inhibiting the prostaglandin COX-2.

Therapeutic Recommendation

Valdecoxib is one of several COX-2 inhibitors used for treatment of osteoarthritis, adult rheumatoid arthritis, and primary dysmenorrhea. Several studies have shown similar reductions in the signs and symptoms of osteoarthritis and rheumatoid arthritis with valdecoxib 10 mg daily when compared with naproxen 500 mg twice daily and placebo. Likewise, ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily have been compared in osteoarthritis patients with similar results. Also, studies have shown that valdecoxib resulted in an incidence of endoscopic gastroduodenal ulcers similar to placebo with about 1/3 the

rate of endoscopic ulcers compared to naproxen 500 mg twice daily, ibuprofen 800 mg three times daily, and diclofenac 75 mg twice daily. Other selective COX-2 inhibitor competitors include celecoxib and rofecoxib with indications and dosages listed in table 1.

Dosing and Administration

Valdecoxib is available in 10 mg (white with "10" debossed on one side and a four point star shape on the other side) and 20 mg (white with "20" debossed on one side and four point star on the other side) tablets for oral use. Valdecoxib can be taken with or without food and with antacids. The recommended dosage of valdecoxib for arthritis is 10 mg daily. The recommended dosage for dysmenorrhea is 20 mg twice daily as needed. Acute overdose of NSAIDs and related compounds cause drowsiness, nausea, vomiting, bleeding of the stomach and stomach pain. Acute renal failure, respiratory depression, and coma are rare in cases of overdose, but can occur. Doses of 20 mg and 40 mg twice daily have been evaluated in knee-replacement surgery and have been effective at reducing morphine consumption 48 hours after surgery. The once daily dosing of valdecoxib may improve patient compliance versus the multiple dosing of traditional NSAIDs.

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Indications and Dosages (Table 1)

	Bextra®	Vioxx®	Celebrex®
Osteoarthritis	10 mg daily	12.5-25 mg daily	200 mg daily*
Rheumatoid arthritis	10 mg daily	----	100-200 mg twice daily
Adenomatous colorectal polyp number reduction	----	----	400 mg twice daily^^
Primary dysmenorrhea	20 mg twice daily as needed	50 mg daily**	----
Acute pain	----	50 mg daily**	----

* May be taken in divided dose (i.e. 100 mg twice daily).

^^Patients must take two 200 mg capsules twice daily and continue standard familial adenomatous polyposis (FAP) therapy. Patients should be instructed to take the two capsules with food.

** Use of Vioxx in the management of acute pain>5 days has not been studied.

Cost Comparison

Medication/Dose	Cost [^]		
	<u>CVS</u>	<u>KMart</u>	<u>Rite Aid</u>
Vioxx® (rofecoxib) 25 mg	93.99	76.39	87.99
Bextra® (valdecoxib) 10mg	103.99	80.99	93.99
Celebrex® (celecoxib) 200 mg	85.59	77.99	81.99

[^]Pricing information represents a 30-day supply of the recommended dosage for osteoarthritis



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Contraindications

Patients who have had asthma, urticaria, or allergic-type reactions after taking aspirin, NSAIDs, or other COX-2 inhibitors should not take valdecoxib due to the possibility of fatal, anaphylactic-like reactions that can occur. Also, valdecoxib and rofecoxib are not contraindicated in patients allergic to sulfa drugs, unlike celecoxib. Analyses suggesting increases in thrombotic cardiovascular events with COX-2 inhibitors are controversial and will require future, prospective trials for elucidation. Likewise, recent data suggests that hypertension development may be more common with certain COX-2 inhibitors, but no definitive results are available at this time.

Special Populations

Geriatrics: Although steady-state concentrations are approximately 30% higher in patients > 65 years of age, there is no dosage adjustment required.

Pediatrics: There are no trials supporting use of valdecoxib in patients under the age of 18.

Pregnancy: Valdecoxib should be avoided in late pregnancy to avoid premature closure of the ductus arteriosus.

Hepatic Insufficiency: Concentrations of valdecoxib are increased approximately 130% in patients with moderate (i.e. Child-Pugh class B) hepatic failure, therefore valdecoxib should be used with caution in these patients. This drug is not recommended in patients with severe hepatic impairment. Doses used that exceed the recommended doses have led to fluid retention in clinical trials. Therefore, caution should be exercised when starting patients with moderate hepatic impairment and fluid retention on valdecoxib.

Renal Insufficiency: There is no need for dosage adjustment in renal failure or patients receiving hemodialysis. Since NSAIDs have been correlated with worsening kidney function, valdecoxib should not be used in advanced renal disease.

Drug Interactions

Valdecoxib is metabolized by the Cyp P450 enzymes 3A4 and 2C9. When administered with a CYP 2C9/3A4 inhibitor, such as ketoconazole, the total plasma exposure of valdecoxib was in-

creased. Valdecoxib is also a weak inhibitor of CYP 2C9. When given with warfarin, there was a small increase in plasma concentrations of warfarin and in the INR, which was statistically significant. Lithium levels may also increase when taken with valdecoxib, therefore lithium levels should be monitored.

Adverse Effects

Some of the adverse effects of valdecoxib include headache, dizziness, abdominal pain, diarrhea, nausea, dyspepsia, constipation, and dry mouth.

Pharmacology

Mechanism of Action: Valdecoxib inhibits prostaglandin synthesis mainly by inhibiting cyclooxygenase-2 (COX-2). At therapeutic concentrations, it does not inhibit cyclooxygenase-1 (COX-1), which causes the adverse effects of non-selective NSAIDs.

Absorption/Distribution: The absolute bioavailability of oral valdecoxib is approximately 83% and reaches maximum plasma concentration in about 3 hours. The AUC does not increase in a proportional manner with multiple doses greater than 10 mg twice daily. Steady state concentrations can be reached by day 4 of treatment. Valdecoxib is approximately 98% protein bound and has a steady state volume of distribution of about 86 L.

Metabolism/Excretion: Valdecoxib is metabolized by the CYP 450 enzymes 2C9 and 3A4 as well as non-P450 pathways (glucuronidation). Therefore, administration with CYP 450 inhibitors may increase valdecoxib levels. Valdecoxib has one active metabolite that is 10% of the concentration of the parent compound and most likely doesn't contribute to the efficacy of valdecoxib. Hepatic metabolism is the main elimination route with less than 5% eliminated unchanged in the kidneys and feces. The half-life is 8-11 hours and the apparent oral clearance (CL/F) is approximately 6 L/hr.

Patient Information

1. Notify your doctor of signs and symptoms of gastrointestinal ulceration or bleeding, skin rash, abdominal pain, bloody stools, or swelling occur.
2. Signs and symptoms of liver toxicity should be monitored. Notify your doctor if nausea, fatigue, jaundice, or flu-like symptoms occur.

3. Take as directed by your physician. Contact your physician if signs of overdosage occur (e.g. drowsiness, nausea, vomiting, GI bleed, etc.).

References:

1. Bextra prescribing information. Pfizer, Pharmacia, Chicago, IL, November 2001.
2. Celebrex prescribing information. Pfizer, Searle, Stokie, IL, April 2000.
3. Vioxx prescribing information. Merck & Co, Whitehouse Station, NJ, May 2001.
4. Dragovich, CM. Chain Pharmacist Practice Memo. Alexandria, VA. 2002;Vol6 (2).
5. Study suggests valdecoxib, a new COX-2 specific inhibitor, is an effective morphine sparing analgesic in knee replacement surgery. (Online). Pharmacia/The Newsroom. www.pharmacia.com [2002, February 26].

Foradil® (formoterol fumarate)

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Introduction

Foradil® [formoterol fumarate, (for-MOT-ter-ol)] was FDA approved in May 2001 for the prevention of exercised-induced bronchospasm and maintenance treatment of asthma and chronic obstructive pulmonary disease (COPD), such as emphysema and bronchitis. Formoterol acts as a beta₂-adrenergic receptor agonist.

Therapeutic Recommendation

Formoterol is an effective long acting, selective beta agonist for use as maintenance asthma and COPD treatment and exercise-induced asthma (EIA). Compared to other beta agonists, formoterol appears to exhibit faster onset and longer duration. Current clinical evidence describes formoterol as having better symptom control over salmeterol.

Aside from efficacy of the agent, cost and flexibility of the dosage form may impede selection of the product. On average, the cost for maintenance dosages of both Foradil® and Serevent®

appear relatively high; however, Serevent® appears to have a slight cost advantage. Also, Serevent® aerosol inhalers allow use of spacers which may show utility in both the pediatric and geriatric populations. For geriatric patients with arthritis or other movement impediments, preparing Foradil® for inhalation may be tedious, if not impossible. Careful matching of patient characteristics with external factors should allow greater adherence with therapy and increased quality of life.

Unlike standard aerosol canisters, Foradil® offers a unique dry powder inhaler apparatus for preparing and delivering the dose. Patients should be educated on how to properly puncture the capsule for delivery, administer the dose, and maintain the device for future doses. This education process should be ongoing and consist of frequent patient follow-up.

When administered two hours before exercise, formoterol retained comparable efficacy to albuterol. In EIA, formoterol's main advantage over albuterol was the duration of action, which could range from 8 to 12 hours. However, cost may play a role in whether or not formoterol is best for a specific patient. The cost of formoterol is approximately three times more than generic albuterol. With such a cost disparity, adherence with formoterol may be problematic for patients who previously used albuterol. Obtaining patient-specific information on lifestyle and exercise can assist in tailoring therapy.

Dosing and Administration

Foradil® is supplied as in a blister pack containing 18 or 60 clear capsules with formoterol fumarate powder. Each unit dose capsule should be used with the Aerolizer® inhaler, which is included with the capsules. These capsules are NOT for oral administration. The administration should be accomplished as described in the *Patient Instruction for Use* insert. Only Foradil® capsules should be used in the inhaler, and the capsules should not be broken out of the blister pack until time of administration.

For maintenance dose treatment of asthma, the usual dose is one capsule (12 mcg) inhaled every

12 hours using the Aerolizer® inhaler. This dose has been studied in adults and children 5 years and older. The manufacturers have not recommended more frequent or higher dosing of formoterol to treat asthma; furthermore, no clinical evidence has been provided to show benefits of increased doses or frequency. For patients who develop symptoms between doses, a short-acting beta₂ agonist, such as albuterol, is suggested for relief of these symptoms. Formoterol may be used with short-acting beta₂ agonists, inhaled or oral corticosteroids, or theophylline to maintain adequate control of symptoms.

In the prevention of EIA, one capsule (12 mcg) has been suggested 15 minutes before exercise. This dose should be administered with the Aerolizer® inhaler on a PRN basis. This dose is approved for adults and children 12 years of age and older.

Cost Comparison

Medication/Dose	Cost*		
	Formoterol (Foradil®)	Salmeterol (Serevent®)*	Albuterol (Warrick)
	2puffsevery 12hours	2 puffs every 12 hours	1-2puffsevery 4-6 hours as needed
CVS	89.99	87.59	24.99
KMart	75.97	87.79	22.99
Kroger	82.59	88.09	18.99
Rite Aid	94.99	79.64	22.41
WalMart	74.78	70.98	17.54

*The Serevent Diskus® device is not reflected by these prices. *Cost represents price to the patient for one inhaler. Foradil and Serevent reflect thirty -day supplies at maintenance doses for asthma. Only albuterol represents generic pricing. Foradil and Serevent are not currently available in generic formulations.

General Precautions

Caution should be exercised in patients with coronary insufficiency, cardiac arrhythmias, hypertension, convulsive disorders, thyrotoxicosis, and those who are unusually sensitive to sympathomimetic amines. If any of these conditions are aggravated or intensified by formoterol, dose reduction or discontinuation should be considered.

Changes in blood pressure, pulse rate, and electrocardiogram are infrequent with formoterol in controlled clinical studies. Patients should be informed of the possibility of these effects and how to monitor them.

Contraindications

Formoterol is contraindicated in any patients who have known hypersensitivity to formoterol fumarate or any other components of the product.

Special Populations

Hepatic impairment, Renal impairment, Geriatrics: The pharmacokinetics of formoterol have not presently been studied in these populations. Dosage adjustment is not currently recommended.

Pediatric: Limited data have been established in this population. One study of children 5 to 12 years showed doses of 12 mcg or 24 mcg twice daily did not significantly exceed the accumulation index of adults based on recovery of unchanged and conjugated formoterol in the urine. Dosage adjustment is not currently recommended and caution should be exercised when administering to this population.

Pregnancy, Lactation: The pharmacokinetics of formoterol have not presently been studied in these populations. Formoterol is rated as pregnancy category C. Caution should be exercised in using formoterol in these populations.

Drug Interactions

No highly significant drug-drug interactions have been found with formoterol; however, caution should be exercised with adrenergic agents, which potentially can increase the sympathetic effects of formoterol.

Xanthine derivatives, steroids, or non-potassium sparing diuretics may increase the risk of hypokalemia when administered concomitantly with adrenergic agents.

Monoamine oxidase inhibitors, tricyclic antidepressants, cisapride, quinine, and procainamide*, when administered along with a beta agonist, have the potential to increase the risk of QTc prolongation, which may lead to ventricular arrhythmias. The extent of this interaction has not specifically been studied with formoterol. (*This is not an all-inclusive list of QTc prolonging agents)

Beta-adrenergic receptor antagonists (Beta-blockers)

These agents may counteract the effect of the beta agonist, and increase the risk of broncho-

spasm in asthmatic patients. Under certain circumstances, these agents may be administered together, but cardioselective agents should be considered, depending on the indication. Caution should be exercised when any beta-adrenergic receptor antagonist is concomitantly prescribed.

Adverse Effects

In placebo-controlled, multi-dose clinical trials of 1,985 patients, adverse reactions were observed with 12 mcg of formoterol twice daily. Adverse events with a frequency greater than 1% were reported. These adverse events, compared to placebo, included: chest infection (2.7>0.4), dyspnea (2.1>1.7), tremor (1.9>0.4), insomnia (1.5>0.8), tonsillitis (1.2>0.7), and rash (1.1>0.7). The frequency of tremors, dizziness, and dysphonia increased as dose was increased from 6 mcg, 12 mcg, and 24 mcg twice daily.

Pharmacology

Mechanism of Action: In the lungs, beta₂ adrenergic pathways are responsible for relaxation of bronchial smooth muscle and inhibition of the release of immediate hypersensitivity mediators from mast cells. Formoterol is 200 times more specific for beta₂ than beta₁ receptors in the body. Along with this specificity, the local activity of formoterol in the lungs allows this agent to relax bronchial smooth muscle, and to some extent, prevent release of some hypersensitivity mediators through stimulation of intracellular adenyl cyclase.

Absorption/Distribution: Formoterol is rapidly absorbed, resulting in a peak concentration within 5 minutes. Due to the inherent nature of the inhaled dosage form, some absorption may occur in the gastrointestinal tract as the medication is swallowed during administration. In vitro, formoterol binds 61-64% to plasma proteins. More specifically, binding to albumen is between 31 and 38%.

Metabolism/Excretion: Formoterol is partially metabolized by CYP2D6, CYP2C19, CYP2C9, CYP2A6 into O-demethyl-formoterol. Clinical evidence does not suggest that drug interactions via these enzymes occur. The unchanged drug or metabolite may be conjugated by glucuronidation. Approximately 10% of the unchanged parent drug and 15-18% of the direct glucuronide conjugate are excreted in the urine, and excretion in feces is minimal. The elimination half-life of formoterol is approximately 10 hours.

Patient Information

1. You should learn how to administer the inhaled dosage form correctly. The *Patient Information for Use* insert provides information on using the inhaler. This documentation needs to be covered with both the primary care provider and the pharmacist to ensure the most beneficial effects of therapy.
2. Foradil® should be used as directed on the label. *The medication is long acting, and should NOT be used for rescue therapy.* Short-acting beta2 agonists, such as albuterol, should be prescribed simultaneously.
3. Foradil®, when used for exercise-induced asthma, should be administered 15 minutes before exercise. Additional doses should not be administered until 12 hours after the initial dose.
4. You need to understand how to administer Foradil® with other inhaled medications, such as inhaled corticosteroids. Typically, you should administer Foradil® before your corticosteroid dose. Allow up to five minutes between puffs.
5. Foradil may cause tremors, chest pain, palpitations, rapid heart rate, tremors, or nervousness. You need to be aware of the possibility of these effects. If the symptoms become bothersome, the primary care provider should be contacted.
6. Do not use a spacer device along with this dosage form. Exhaling into the inhaler may cause ineffective administration of a dose.
7. Keep the capsules in the blister pack in a cool, dry place. The capsules should only be taken from the blister pack with dry hands at the time of administration.
8. If you are pregnant or nursing, advise your primary care provider immediately.
9. The capsule should only be punctured once, and the capsules should be kept in cool, dry places. Following these suggestions prevents tiny pieces of gelatin, not retained by the screen inside the device, from entering the throat or mouth.
10. This medication is not a substitute for other types of medication, such as inhaled corticosteroids. Only the primary care provider should change or discontinue treatment.

References:

1. Foradil® prescribing information. Novartis Pharmaceuticals, Inc., East Hanover, NJ, Sept 2001.
2. Formoterol (Foradil Aerolizer®) for Asthma. *The Medical Letter* 2001;43(1104):39-40.
3. Bartow RA, Brogden RN. Formoterol: update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998;55(2):303-22.
4. Cazzola M, Donner CF. Long acting beta2 agonists in the management of stable chronic obstructive pulmonary disease. *Drugs* 2000 Aug;60(2):307-20.

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