

NEW DRUG UPDATE



August 2003

Volume IX, Issue 4

West Virginia University · Charleston Division

EDITOR-IN-CHIEF - Kristy Lucas, Pharm.D.

CO-EDITOR - Greg Rosencrance, M.D.

MANAGING EDITOR - Tara White

Abilify® (aripiprazole)

Authors

Missi Latocha, Pharm.D.

Clinical Pharmacy Resident
West Virginia University – Morgantown

Kristy Lucas, Pharm.D.

Clinical Assistant Professor
Schools of Pharmacy and Medicine
West Virginia University - Charleston

Introduction

Abilify (aripiprazole (ari-pi-PRAY-zol), is a new psychotropic agent whose mechanism of action differs from other available antipsychotic agents. It was approved in November 2002. Aripiprazole is indicated for the treatment of schizophrenia.

Therapeutic Recommendation

Aripiprazole is a novel antipsychotic drug with a different mechanism of action compared to other available typical and atypical antipsychotics. The efficacy of aripiprazole is thought to be a result of dopamine (D) antagonism at the D₂ receptors in the mesolimbic pathway, partial agonist activity at D₂ receptors in the mesocortical pathway, strong antagonism of 5-HT_{2A} receptors and also agonistic activity at 5-HT_{1A} receptors. Aripiprazole is thought to be a dopamine system stabilizer, which results in a decreased amount of side effects. Aripiprazole has efficacy for both positive and negative symptoms because of the combination of effects to the dopamine serotonin system. These combined mechanisms may also be the reason for the low side effects of this drug. Clinical trials have shown aripiprazole is superior to placebo. In a 4-week trial, aripiprazole 15 to 30 mg had similar efficacy to

risperidal 6 mg. The aripiprazole group showed faster improvement in negative symptoms than those in the risperidal group. In a 4-week trial comparing aripiprazole and haloperidol to placebo, both haloperidol and aripiprazole were superior to placebo. Aripiprazole had similar efficacy to haloperidol however, aripiprazole was superior in alleviating negative and depressive symptoms. The most common side effects reported with haloperidol included extrapyramidal symptoms and somnolence while the most common side effect of aripiprazole was nausea. The incidence of discontinuing treatment as a result of adverse effects was similar between the aripiprazole and placebo groups. Aripiprazole treatment has been associated with minimal weight gain and has not been associated with QT_c prolongation or hyperprolactinemia. This drug has shown efficacy in improving both positive and negative symptoms. Aripiprazole also has minimal side effects. This may be beneficial when deciding on treatment.

Dosing and Administration

Aripiprazole is available in 10 mg (pink/rectangular), 15 mg (yellow/round), 20 mg (white/round), and 30 mg (pink/round) tablets for oral administration. The recommended starting dose and maintenance dose of aripiprazole is 10 to 15 mg once daily given without regards to meals. Aripiprazole can be titrated up to 30 mg once daily, however larger doses have not proven to be

Inside This Issue:

- Abilify® (aripiprazole)
- Relpax® (eletriptan)
- Tracleer® (bosentan)

more effective than the lower doses. Dosage titration should not occur prior to two weeks of treatment due to the extended half-life. Patients should be re-evaluated periodically regarding their need for long-term maintenance therapy. No evidence is available for long-term use of aripiprazole. Dosage adjustments are not necessary based on patient's age, gender, race, hepatic or renal impairment.

Cost Comparison

Medication/Dose	Cost*		
	CVS	Drug Emporium	Kroger
Geodon® (ziprasidone) 20 mg BID	289.99	252.23	307.59
Risperdal® (risperidone) 1mg BID	220.99	183.13	227.99
Zyprexa® (olanzapine) 5 mg QD	195.99	177.44	219.19
Seroquel® (quetiapine) 100 mg TID	285.99	256.38	300.09
Abilify® (aripiprazole) 15 mg QID	339.99	308.37	362.79

*Cost to patient for a 30-day supply at the initial starting dose

Warnings

Psychotropic agents are known to cause neuroleptic malignant syndrome (NMS), which is potentially fatal. If a patient requires antipsychotic drug therapy following recovery from NMS, treatment should carefully be considered along with close monitoring. Tardive dyskinesia (TD) is also associated with the use of psychotropic agents. The likelihood of TD occurring increases with

prolonged duration of therapy and increased doses of the psychotropic medication.

Contraindications

Aripiprazole is contraindicated in patients who have a known hypersensitivity to aripiprazole or any of its components.

Special Populations

Pregnancy: Aripiprazole is classified as a category C agent. Animal studies have shown that aripiprazole resulted in developmental toxicity and also mutagenesis. Aripiprazole should only be used in pregnant women when benefit outweighs risk.

Lactation: Aripiprazole was excreted in milk during lactation in rats. It is not known if aripiprazole or its metabolites are excreted in human breast-milk therefore, breast-feeding is not recommended.

Pediatrics: Safety and efficacy have not been established in this population.

Geriatrics: There appears to be a slight decrease in clearance in the elderly population but dosage adjustment is not necessary. In treating psychosis in patients with Alzheimer's, studies have shown a different tolerability profile. There has been an increased incidence of side effects. Aripiprazole was associated with somnolence in a dose related fashion. Safety and efficacy have not been established in this group. If the prescriber elects to treat these patients with aripiprazole, caution should be exercised.

Hepatic Impairment: The AUC of aripiprazole was altered depending on varying degrees of impairment but dosage adjustment is not necessary.

Renal Impairment: No dosage adjustment is recommended in patients with renal insufficiency. Renal excretion of aripiprazole is less than 1% of the dose.

Drug Interactions

Aripiprazole is metabolized through CYP3A4 and CYP2D6. Inducers of CYP3A4 may cause and increase in clearance and a decrease in the blood level of the drug. Inhibitors of CYP3A4 may result in a decreased clearance and an increased blood level. Administration with ketoconazole, a potent CYP3A4 inhibitor, resulted in a 63% and 77% increase of the AUC of aripiprazole and dehydro-aripiprazole, a metabolite. Quinidine, a potent CYP2D6 inhibitor, resulted in a 112% increase of the AUC of aripiprazole and a 35% decrease in the AUC of dehydro-aripiprazole. Carbamazepine, a potent CYP3A4 inducer, caused a decrease in the AUC and C_{max} of ~70%. Aripiprazole had no significant effect on alcohol, famotidine, valproate, lithium, dextromethorphan, warfarin or omeprazole. No



...A Primary Care Physician's Guide to Newly Released Medications...

Departments of Internal Medicine and Clinical Pharmacy West Virginia University Charleston Division

Robert C. Byrd Health Sciences Center
3110 MacCorkle Ave., SE
Charleston, WV 25304
(304) 347-1377

Fax: (304) 347-1350

E-mail: klucas@hsc.wvu.edu

Visit New Drug Update online at:
www.hsc.wvu.edu/charleston/sopc/nduhome.html

dosage adjustments are necessary when used with these agents. Aripiprazole should be used with caution when taken with certain antihypertensive drugs i.e., doxazosin, terazosin, prazosin, carvedilol, and labetalol, because of alpha-adrenergic receptor antagonism.

Adverse Effects

The most common adverse event associated with aripiprazole included: headache, anxiety, insomnia, nausea, vomiting, lightheadedness, somnolence, akathisia, and constipation. Other adverse events reported with aripiprazole include asthenia, rash, and also orthostatic hypotension. Extrapyramidal side effects occurred similarly in aripiprazole and placebo. Aripiprazole had no significant effect on the QT_c interval.

Pharmacology

Mechanism of Action: Aripiprazole is thought to act as a dopamine system stabilizer. Aripiprazole exhibits partial agonism at D₂ receptors. It is a D₂ antagonist in the mesolimbic pathway and a partial D₂ agonist in the mesocortical pathway. Aripiprazole also has 5-HT_{2a} antagonism and 5-HT_{1a} agonism. Aripiprazole has moderate affinity for alpha-adrenergic receptors, histamine receptors, D₄, 5-HT_{2c}, 5-HT₇, and serotonin reuptake sites. This drug has low affinity for cholinergic and muscarinic receptors.

Absorption/Distribution: Following oral administration, aripiprazole was well absorbed and had a peak plasma concentration occurring in 3 to 5 hours. The absolute bioavailability of a 15 mg tablet is 87%. Aripiprazole and its major metabolite, dehydroaripiprazole, are highly protein bound (>99%), primarily to albumin. Aripiprazole has a volume of distribution of 4.9 L/kg following IV administration.

Metabolism/Excretion: Aripiprazole is metabolized through dehydrogenation, hydroxylation, and N-dealkylation. CYP3A4 and CYP2D6 are responsible for dehydrogenation and hydroxylation and N-dealkylation occurs through CYP3A4. Less than 1% of aripiprazole is excreted unchanged in the urine and ~18% is excreted unchanged in the feces following a single oral dose.

Patient Information

1. Do not take aripiprazole if you are allergic to aripiprazole or any of its components.
2. It may take several weeks before the benefit from the medication is noticed. Do not get discouraged and quit taking your medication or increase the dose. Take the medication exactly as prescribed.
3. The most common side effects that may occur in-

clude headache, nausea, vomiting, and somnolence. Notify your doctor if you experience any serious side effects from this medication.

4. It is important to take the medication at the same time everyday. If you miss a dose take it as soon as you remember. If it is almost time for the next dose simply skip the missed dose. Do not double the dose.
5. Your body may take several days to adjust to this medication. While your body is adjusting, rise slowly from a sitting position. If you rise quickly you may feel dizzy or lightheaded because your blood pressure will drop. Notify your doctor if you experience this problem.
6. Notify your doctor of all medications that you are taking. Some medications may interact with this drug and are unsafe when taken together. Inform your doctor of all over-the-counter products, herbals,

References

1. Abilify[®] prescribing information. Bristol-Myers Squibb Company, Princeton, New Jersey, November 2002.
2. Goodnick PJ, Jerry JM. Aripiprazole: profile on efficacy and safety. *Expert Opin Pharmacother* 2002 Dec;3(12):1773-81.
3. Kane JM, et. al. Efficacy and Safety of Aripiprazole and Haloperidol Versus Placebo in Patients With Schizophrenia and Schizoaffective Disorder. *J Clin Psychiatry* 2002 Sept;63(9):763-71.
4. Kehoe WA. New Drug: Aripiprazole (*Abilify*); *Pharmacist's Letter*, Vol. 18; December 2002.
5. McGavin JK, Goa KL. Aripiprazole. *CNS Drugs* 2002; 16(11):779-86.

Relpax[®] (eletriptan)

Authors: Heather Blevins, Pharm.D.

Beth Wise, Pharm.D.

Oncology Pharmacy Resident
University of Pittsburgh Medical Center

Introduction

Relpax[®] [eletriptan (el-E-trip-tan)], like sumatriptan, is a selective 5-hydroxytryptamine (5-HT) agonist. It was approved by the FDA on December 26, 2002 for acute treatment of migraine headaches (with or without aura) in adults. It is not approved for migraine prophylactic therapy or for treating any other type of headache.

Therapeutic Recommendation

Eletriptan has been proven highly effective in relieving migraines. In eight clinical trials (double-blind, placebo-controlled) eletriptan 40 mg pro-

duced headache control in a significantly greater number of patients compared to placebo. When compared to oral sumatriptan, eletriptan showed similar efficacy. Eletriptan's efficacy is not affected by duration of attack, gender/age of patient, relationship to menses, or concomitant use of estrogen replacement therapy. It is not intended for prophylactic therapy of migraines or treatment therapy of hemiplegic or basilar migraines. Safety and efficacy have not yet been established for cluster headaches. Its mechanism of action is similar to other triptans. Potential therapeutic advantages with eletriptan are rapid absorption and high bioavailability. Eletriptan is well absorbed after oral administration with peak levels occurring approximately 1.5 hours after administration. The absolute bioavailability is approximately 50% compared to sumatriptan's bioavailability of 20%. For migraine sufferers, this rapid absorption and higher bioavailability produce rapid relief of migraines.

Dosing and Administration

Single doses of 20 mg and 40 mg tablets are effective for acute treatment of migraine. In clinical trials, the 40 mg dose had a greater response among the participants. Dosing must be individualized because patients may vary in their response to eletriptan. A second dose may be beneficial if the first dose does not provide relief. The second dose should be taken at least two hours after the initial dose.

Doses of 80 mg are effective, but are associated with increased incidence of adverse events. Thus, 80 mg tablets were not approved by the FDA. Maximum dose per day is 80 mg.

- Age less than 18 years
- Use within 24 hours of a different 5-HT agonist (to prevent serotonin syndrome)

Contraindications

- Ischemic heart disease (angina pectoris, MI, silent ischemia)
- Symptoms consistent with ischemic heart disease
- Cerebrovascular syndromes (stroke, TIA)
- Peripheral vascular disease
- Uncontrolled hypertension
- Hemiplegic or basilar migraine
- Severe hepatic impairment
- Hypersensitivity to eletriptan or any of its inactive ingredients

Special Populations

Renal Impairment: No significant change in clearance has been observed with mild, moderate, or severe renal impairment. However, increased blood pressure was observed.

Hepatic Impairment: Severe hepatic impairment has not been evaluated. Patients with mild and moderate hepatic impairment had an increase in AUC by 34% and an increase in half-life.

Pregnancy: There have been no adequate and well-controlled studies in pregnant women taking eletriptan. Pregnant women should only take eletriptan if the benefits outweigh the risks. Eletriptan carries a pregnancy category C.

Lactation: Eletriptan is excreted in breast milk. Over a 24 hour period, 0.02% of an 80 mg dose is detected. Caution should be used.

Pediatrics: Safety and efficacy has not been established in pediatric patients, therefore eletriptan is not recommended.

Geriatrics: Eletriptan has only been studied in 50 patients over the age of 65. Eletriptan increased blood pressure in this population. No differences were noted in adverse reactions versus those under the age of 65.

Drug Interactions

Eletriptan is metabolized by the CYP450 3A4 enzyme. Eletriptan should not be used within 72 hours of taking a CYP450 3A4 inhibitor (ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, etc...). Interactions with drugs metabolized by other CYP450 enzymes have not been studied.

Ergot-containing (dihydroergotamine [DHE], methysergide) drugs have been shown to cause prolonged vaso-spastic reactions. Use of eletriptan with these drugs is

Cost Comparison

Medication/Dose	Cost*		
	CVS	KMart	Kroger
Amerge® (naratriptan)	177.18	157.94	138.54
Axert® (almotriptan)	111.99	91.97	82.63
Frova® (frovatriptan)	224.04	187.92	172.92
Imitrex® (sumatriptan)	175.98	147.94	121.95
Maxalt® (rizatriptan)	165.98	147.94	121.95
Relpax® (eletriptan)	140.99	131.96	146.79
Zomig® (zolmitriptan)	87.00	69.80	62.72

*Cost to patient for a 30-day supply (4 attacks at maximum dose)

Warnings/Precautions

- Pregnancy
- Breastfeeding
- Hepatic impairment

not recommended and patients should wait at least 24 hours between administrations.

Propranolol increases the C_{max} and AUC of eletriptan without increasing blood pressure. Dosage adjustment is needed in patients taking propranolol and eletriptan concurrently.

Adverse Effects

Serious cardiac events are rare but can be fatal. These include coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

Cerebrovascular events have also been reported in patients using 5-HT agonists. These include cerebral hemorrhage, subarachnoid hemorrhage, and stroke.

Vasospastic reactions other than coronary have also been reported. Peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been documented.

Increases in blood pressure have been rarely reported in patients with and without a history of hypertension. Oral eletriptan has been shown to cause small, transient increases in blood pressure, primarily diastolic. Renally-impaired patients experienced this increase to a greater extent.

General side effects include back pain, chills, dizziness, nausea, and fatigue.

Pharmacology

Mechanism of Action: Eletriptan is a 5-HT receptor agonist, with high affinity to 5-HT 1B/1D/1F receptors. It has moderate affinity to 5-HT 1A/1E/2B/7 receptors with minimal affinity to 5-HT 2A/2C/3/4/5A/6 receptors. Migraine relief is believed to involve 5-HT 1 receptors primarily. Two explanations of the mechanism of eletriptan exist. First, activation of these receptors located on cranial blood vessels leads to vasoconstriction, the mechanism associated with the relief of migraine. Second, activation of these receptors on sensory nerve endings in the trigeminal system leads to inhibition of proinflammatory neuropeptide release.

Absorption/Distribution: After oral administration, eletriptan has peak plasma levels 1.5 hours after dose. In patients with moderate to severe migraines, the median T_{max} is 2.0 hours. Mean absolute bioavailability is approximately 50%. The AUC and C_{max} are increased by 20-30% with administration following a high fat meal. The volume of distribution with IV administration is 138 L. Protein binding is approximately 85%.

Metabolism/Excretion: Eletriptan is metabolized by N-demethylation to an active metabolite that can cause vasoconstriction similar to the parent compound. The

half-life of the metabolite is approximately 13 hours and the plasma concentration of the metabolite is 10-20% of the parent compound, making it unlikely to add to the benefits of the parent compound. Eletriptan is metabolized primarily by CYP450 3A4. The terminal half-life of eletriptan is approximately 4 hours. Only 10% of eletriptan is renally cleared.

Patient Information

1. Eletriptan is indicated for relief of migraine headaches only and is not to be used to treat cluster headaches or any other type of headache.
2. Eletriptan is generally well tolerated. Side effects are usually mild and are not generally long lasting. Some of the common side effects include dizziness, nausea, weakness, tiredness, and a pain or pressure sensation in the chest or throat. Rarely, eletriptan will cause serious side effects that include severe chest pain and shortness of breath leading to heart attacks. If these side effects are experienced, call physician and discontinue use of medication.
3. Eletriptan is to be taken as soon as a migraine begins. A second dose can be taken if headache does not improve. Wait at least two hours before taking the second dose. Do not take more than two doses (80 mg maximum) in a 24-hour period.
4. Eletriptan should not be taken if any of the following exist:
 - uncontrolled high blood pressure
 - heart disease/history of heart disease
 - hemiplegic or basilar migraine
 - history of stroke
 - liver problems
 - use of other triptans
 - use of ergotamines (Bellegral-S, Cafergot, methysergide)
 - allergy to eletriptan or any of its ingredients

References

1. Relpax® prescribing information. Pfizer Inc., New York, NY. December 2002.
2. Eletriptan. *Expert Opinion of Investigational Drugs* 2001 Oct; 10(10):1869-74.
3. Eletriptan for acute migraine. *Cochrane Database Syst Rev* 2001;(3):CD003224.

Tracleer® (bosentan)

Authors: **Joanna Stollings, Pharm. D.**
Pharmacy Practice Resident
Charleston Area Medical Center
Charleston, WV

Kristy Lucas, Pharm. D.
Clinical Assistant Professor
Schools of Pharmacy and Medicine
West Virginia University - Charleston

Introduction

Tracleer® [bosentan (boe-SEN-tan)] is a specific and competitive non-peptide endothelin receptor antagonist. Bosentan received FDA approval on November 20, 2001 for the oral treatment of pulmonary arterial hypertension (PAH) in patients that experience shortness of breath at rest or with minimal activity (World Health Organization [WHO] Class III or IV).

Therapeutic Recommendation

In the early stages of PAH, smooth muscle hypertrophy and vasoconstriction predominate in lesions. As the disease progresses, the proliferative features of the disease become more dominant and vasodilators lose their effects. Seventy-five percent of patients that are diagnosed with PAH are already in this proliferative phase. Epoprostenol is a synthetic prostaglandin analog that decreases pulmonary vascular resistance in pulmonary arteries. However, due to the short half-life of the drug, it must be administered by continuous intravenous infusion; it also must be kept on ice. Patients may be predisposed to a catheter infection due to the continuous intravenous infusion in the central vein. Treprostinil, another synthetic prostaglandin analog was released in May 2002. It requires continuous administration by a subcutaneous route. Bosentan is an orally administered competitive endothelin-1 antagonist used to decrease pulmonary vascular resistance. A randomized, double-blind, placebo-controlled trial of 32 patients with NYHA class III PAH was conducted. After 12 weeks, six minute walking distance increased by an average of 70 meters in those treated with bosentan 125 mg twice daily versus a 6 meter decrease in 6 minute walking time in those receiving placebo. The BREATHE-1 trial of 213 patients with NYHA class III or IV PAH showed an average increase of 27 meters in a six-minute walking distance when treated with bosentan 125mg twice daily.

Bosentan does seem to be effective in the treat-

ment of PAH. Its oral administration route reduces the risk of infection and is more convenient. All three drugs are very expensive, but there are programs to help with reimbursement. Bosentan does have the potential to have many drug interactions due to its metabolism through the CYP450 system, so patients should be closely monitored. Patients must also be urged about the importance of obtaining regular liver function tests and pregnancy tests to prevent harm.

Dosing and Administration

Bosentan is available as a 62.5 mg and a 125 mg tablet. Patients being treated with bosentan should take 62.5 mg twice daily for four weeks, and then increase to the maintenance dose of 125 mg twice daily. The tablets should be taken in the morning and evening with or without food.

Cost Comparison and Distribution Issues

Bosentan (Tracleer®) 125 mg tablets taken twice daily cost approximately \$35,640 a year. Epoprostenol (Flolan®) requires continuous intravenous infusion due to short half-life and costs approximately \$50,000/year. Treprostinil (Remodulin®) requires continuous subcutaneous infusion. The average dose of treprostinil is 8 to 38 ng/kg/min, which is approximately \$18,000-\$90,000/year (\$65/mg). When comparing the price of bosentan to epoprostenol and treprostinil, one must take into account the supplies that it takes to continuously administer a medication intravenously or subcutaneously. The costs listed above for epoprostenol and treprostinil do not take into account the pumps, catheters, tubing, syringes, or dressings that administration of these medications requires. All three of these medications are rather expensive, especially when one considers that these medications are potential life-long therapy. However, there are reimbursement programs for patients to help them to obtain these medications. Reimbursement for these drugs varies depending on insurance plans, but the manufacturer claims that most insurance companies cover these medications. Due to safety concerns, a closed distribution program is in place for acquisition of bosentan. Only centralized pharmacy systems may dispense the drug. This program mandates appropriate monitoring before subsequent prescriptions are filled. Prescribers can call 1-866-228-3546 for information on distributors and reimbursement assistance.

Warning/Precautions

- Bosentan caused a 3-fold increase in liver enzymes (ALT and AST in)11% of patients studied. Elevated levels of bilirubin have also been seen in a few cases. Liver enzymes must be monitored at

baseline and then monthly thereafter.

- There has been limited experience with abrupt discontinuation of bosentan. Although there has been no evidence of acute rebound in these patients, it is recommended that patients gradually reduce their dose (62.5 mg twice daily for 3 to 7 days).
- Bosentan treatment can cause a dose related decrease in hemoglobin and hematocrit. Levels of hemoglobin should be monitored after one and three months of therapy and every three months thereafter. The average decrease in hemoglobin was 0.9 g/dL. Most of the decrease in hemoglobin concentrations seemed to occur in the first few weeks of treatment. Hemoglobin levels usually stabilized between 4 and 12 weeks of treatment.

Contraindications

Bosentan is contraindicated in patients with any known hypersensitivity to bosentan or any of its components.

Bosentan is categorized as a pregnancy category X medication. Teratogenic effects were demonstrated in rats when bosentan was administered.

Concomitant use of bosentan with cyclosporin or glyburide is contraindicated. (See "Drug Interactions")

Special Populations

Women of childbearing age: Since this is a pregnancy category X agent, women of child-bearing age should only be prescribed bosentan if they can provide negative results from a urine or serum pregnancy test performed during the last five days of her menstrual period AND at least 11 days after having unprotected sexual intercourse. Although specific interaction tests between bosentan and hormonal contraceptives have not been performed, it is possible that co-administration of these two agents might result in the failure of contraception since bosentan and many hormonal contraceptives are metabolized by CYP3A4. Therefore, individuals taking bosentan and hormonal contraceptives also need to be practicing adequate contraceptive measures, not relying only on hormonal contraceptives (oral, injectable, topical or implantable). Two forms of birth control are recommended.

Nursing mothers: It is unknown whether bosentan is excreted in human milk. Therefore, it is not recommended to breastfeed while taking bosentan.

Pediatrics: The safety and efficacy of bosentan use in children has not been established.

Renal impairment: The pharmacokinetics of bosentan are slightly affected in patients with severe renal impairment (creatinine clearance 15-30 ml/min). Bosentan plasma concentrations were unchanged, while concen-

trations of the three metabolites increased two-fold. The change in the concentrations of the metabolites does not appear to be clinically significant, and therefore bosentan dosing does not need to be adjusted.

Hepatic impairment: There is no specific data at this time to guide dosing in patients with liver impairment. However, caution should be used when administering bosentan to patients with mild liver impairment since it undergoes extensive metabolism by the liver. Bosentan administration should be avoided in patients with moderate or severely impaired liver function and/or elevated aminotransferases greater than 3 times the upper limit of normal.

Low body weight: The recommended initial and maintenance dose of bosentan in patients weighing less than 40 kg but older than 12 years of age is 62.5 mg twice daily.

Drug Interactions

Bosentan is metabolized by CYP2C9 and CYP3A4. Drugs that inhibit these enzymes can lead to increased concentrations of bosentan. Ketoconazole, a potent CYP3A4 inhibitor increased the concentration of bosentan 2-fold in one trial. Cyclosporin-A co-administration with bosentan increased the concentration of bosentan 30-fold the first day. The co-administration of cyclosporin-A and bosentan is contraindicated.

Co-administration of glyburide and bosentan is contraindicated due to the increased risk of having elevated liver enzymes.

Bosentan also is an inducer of CYP3A4 and CYP2C9. Co-administration of bosentan and drugs metabolized by these enzymes will result in decreased levels of these drugs. For example, bosentan has been shown to decrease levels of simvastatin and warfarin through these pathways.

Adverse Effects

Liver enzymes (AST, ALT) were elevated to 3 times their normal value in 11% of patients receiving bosentan. Hemoglobin and hematocrit was decreased by at least 1 g/dl in 57% of patients receiving bosentan versus 29% receiving placebo. Headache, facial flushing, and leg edema were more common with bosentan, as well.

Pharmacology

Mechanism of Action: Bosentan acts as a competitive antagonist at endothelin-1 (ET-1) receptors ET_A and ET_B. ET_A receptors are found in vascular smooth muscle, while ET_B receptors are located in the brain, endothelium, and smooth muscle cells. ET-1, a strong

vasoconstrictor with proliferative, profibrotic, and pro-inflammatory effects, is found in elevated concentrations in the plasma and lung tissue of individuals with PAH. Bosentan's antagonism of the ET-1 receptors decreases pulmonary vascular resistance and lessens the effects of chronic hypertension on vascular remodeling.

Absorption/Distribution: Bosentan's absolute bioavailability is not affected by food and is about 50%. Peak plasma concentrations of bosentan are reached within three to five hours. Bosentan's volume of distribution is approximately 18L. Bosentan is highly bound (>98%) to plasma proteins, albumin primarily. Erythrocyte penetration is not seen with bosentan.

Metabolism/Excretion: Bosentan is metabolized in the liver and has three metabolites. Only one of these is pharmacologically active, contributing to 10-20% of bosentan's effects. Bosentan induces CYP2C9 and CYP3A4. The total clearance of bosentan after a single intravenous administered dose is 8 liters per hour. Following multiple doses of bosentan, plasma concentrations of the drug decrease to 50 to 65% of that following single dose administration. Elimination of

bosentan occurs by biliary excretion from the liver. Bosentan has a terminal elimination half life of approximately 5 hours. Less than 3% of the oral dose administered is found excreted unchanged in the urine.

Patient Information

1. Bosentan should be taken twice daily. It should be taken in the morning and evening without regards to food.
2. Monthly levels of liver enzymes must be obtained.
3. Bosentan can be harmful to the fetus if a woman gets pregnant. Although specific interaction tests between bosentan and hormonal contraceptives have not been performed, it is possible that co-administration of these two agents might result in the failure of contraception. Therefore, individuals taking bosentan and hormonal contraceptives need to get monthly pregnancy tests and use an additional form of contraception, rather than relying solely on hormones (oral, injectable, topical, and implantable). Reimbursement programs are available through most insurance companies to enable patients to obtain this costly medication.

References

1. Medical Letter 2002;44:30-32.
2. Rubin LJ et al. Bosentan therapy for pulmonary arterial hypertension. *NEJM* 2002; 346:896-903.
3. <http://www.unither.com>
4. Bosentan Product Information. Actelion Pharmaceuticals. 2001
5. Gaine S. Pulmonary Hypertension. *JAMA* 2000; 284:3160-3168.



Departments of Internal Medicine
and Clinical Pharmacy
WVU - Charleston Division
Robert C. Byrd Health Sciences Center
3110 MacCorkle Ave., SE
Charleston, WV 25304

PRST STD
U.S. Postage
PAID
Permit #169
Charleston, WV 25301