

NEW DRUG UPDATE

December 2002

Volume VIII, Issue 6



West Virginia University · Charleston Division

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Frova® (frovatriptan)

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Introduction

Frova® [frovatriptan (frov-a-TRIP-tan)] is a 5-HT receptor agonist that selectively binds to 5-HT 1B and 5-HT 1D receptors. It was approved in November 2001 for the acute treatment of migraine attacks with or without aura in adults.

Therapeutic Recommendation

Frovatriptan has a similar mechanism of action and efficacy profile as other drugs in its class, but its extended half-life makes it more appealing for some migraine sufferers. Frovatriptan has a 26-hour half-life, compared to other triptans with half-lives of up to 6 hours. Since migraines last 4-72 hours, patients not receiving relief for the duration of their migraine with conventional medications may benefit most from frovatriptan. Additionally, frovatriptan may be useful for sufferers of slow-onset attacks or menstrual migraines. When compared to suma-

triptan frovatriptan produced migraine relief less rapidly, but more effectively prevented recurrences.

Dosing and Administration

The normal dose of frovatriptan is 2.5 mg to 5 mg orally, and the medication is available as 2.5 mg tablets only. The manufacturer recommends repeating the dose if no headache relief has been achieved two hours after the initial dose. The maximum dose per day is 7.5 mg.

Cost Comparison

Medication/Dose	Cost*		
	CVS	KMart	Rite Aid
Frova® (frovatriptan)	224.04	187.92	172.92
Axert® (almotriptan)	111.99	91.97	82.63
Imitrex® (sumatriptan)	175.98	147.94	119.73
Zomig® (zolmitriptan)	87.00	69.80	62.72
Maxalt® (rizatriptan)	165.98	147.94	121.95
Amerge® (naratriptan)	177.18	157.94	138.54

*Prices shown indicate a one month supply assuming maximum dose for 4 attacks per month.

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Contraindications

Frovatriptan is contraindicated in patients with uncontrolled high blood pressure, ischemic heart disease, history of stroke, circulation problems, peripheral vascular disease, including ischemic bowel disease, hemiplegic or basilar migraine, or a previous hypersensitivity to frovatriptan or any of its components.

Precautions

Caution should be used when the patient is breastfeeding or pregnant, has renal or hepatic impairment, has ischemic or vasospastic coronary artery disease, or if the patient has unrecognized coronary heart disease with diabetes, obesity, cigarette smoking, high cholesterol, strong family history of coronary artery disease, is a male older than 40 years old, or a postmenopausal woman. Caution should also be used in those patients who have previously been undiagnosed with migraines or those who present with atypical symptoms.

Special Populations

Geriatrics: No specific adjustments need to be made, but caution should be used. The serum concentrations of frovatriptan are 1.5 to 2 fold higher in elderly than in younger patients.

Pediatrics: Dosing and pharmacokinetic parameters have not been evaluated in pediatric patients (less than 18 years old).

Hepatic impairment: Since frovatriptan is not significantly cleared hepatically, no dosing adjustment is required. Studies have not been performed in this population, but the lowest dose possible (2.5 mg) should be used.

Renal impairment: Dosing adjustment is also not required for renally impaired patients. Only about 10% of the drug is eliminated renally; however, the lowest possible dose should be used (2.5 mg).

Pregnancy: Frovatriptan has not been studied in pregnancy, therefore it should be used with extreme caution. If it must be used, use the lowest dose possible. It is currently rated Pregnancy Category C.

Lactation: It is not known if frovatriptan is excreted in human breast milk; however, the drug did pass through in primate studies. Frovatriptan should be used with caution in lactation.

Drug Interactions

Concomitant administration with any other serotonin agonist within 24 hours is contraindicated. The combination may cause an increased risk of serotonin syndrome.

Concomitant administration with any ergotamine-containing or ergot-type medication, such as dihydroergotamine or methysergide, within 24 hours is contraindicated. Ergot alkaloids can increase or prolong vasospastic reactions.

MAO inhibitors decrease the clearance of frovatriptan, increasing the risk of systemic toxic effects. Concurrent use of or use within 2 weeks of discontinuing MAO therapy is contraindicated.

Adverse Effects

Although some potentially fatal side effects may occur, the likelihood and incidence of these are very low. The most serious reactions involve cardiovascular effects, including coronary vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.



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Physician's Guide to
Newly Released
Medications...

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These effects have a greater likelihood of occurrence in patients with risk factors for coronary artery disease. Less serious cardiovascular effects include chest pain and flushing.

Other, less serious side effects include dizziness (8%), headache (4%), paresthesia (4%), fatigue (5%), dry mouth (3%), and dyspepsia (2%).

Pharmacology

Mechanism of Action: Frovatriptan is a 5-HT agonist that binds to 5-HT 1B and 5-HT 1D receptors with high affinity. It has no significant effects on GABA-mediated channel activity and does not interfere with benzodiazepine binding sites. Frovatriptan is believed to inhibit excessive dilation of extracerebral intracranial arteries in migraine.

Absorption/Distribution: Frovatriptan has an absolute bioavailability of 24-30 % after oral administration. Absorption is higher in females than in males. Food does not affect the drug's absorption. The mean half-life is about 26 hours.

Metabolism/Excretion: Frovatriptan is primarily metabolized by the liver and is mediated by CYP1A2. It produces one active metabolite, which has a slightly lower affinity for the 5-HT receptors than does its parent compound. Renal elimination accounts for 40% of the drug's total clearance, while, 62% of the drug is eliminated in the feces. The total body clearance in females is lower.

Patient Information

1. Please inform your doctor about any other medications you may be taking. Frovatriptan can have serious interactions with many medications including other serotonin agonists, ergotamine containing medications, or MAO inhibitors. These drugs must be eliminated from your body before frovatriptan therapy can begin.
2. Please inform you doctor about any medical problems you may have, especially problems dealing with your heart. Frovatriptan should not be used in patients with uncontrolled high blood pressure, heart disease, or a history of stroke or other circulation problems. It should also not be used for hemiplegic or basilar migraine headaches.
3. The most common side effects of frovatriptan are dizziness, headache, tingling, fatigue, dry mouth and upset stomach. If you experience any of these effects while taking frovatriptan, you should tell your doctor. If these effects persist or worsen, he or she may discontinue the medication.
4. If you experience any symptoms of heart problems (i.e., tightness, pain, or pressure in your chest), you should seek medical attention immediately and stop taking the medication unless your physician directs you to continue it.

References:

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2. Almotriptan and Frovatriptan for Migraine. *The Medical Letter* 2002 Feb 18;44(1124):19-20.
3. Rapoport AM. Triptans are All Different. *Archives of Neurology* 2001;58(9):1479-80.

Xyrem® (sodium oxybate)

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Introduction

Xyrem® (sodium oxybate) is a central nervous system depressant approved by the FDA in July 2002 for the treatment of cataplexy associated with narcolepsy. Sodium oxybate is a naturally occurring inhibitory neurotransmitter with highest concentrations in the basal ganglia. It binds to gamma aminobutyric acid (GABA)-B receptors as well as sodium oxybate specific receptors. At low doses, dopaminergic activity is reduced, while at high doses, it can stimulate the release of dopamine. It also interacts with serotonin, opiate, and cholinergic receptors. The precise mechanism of action by which it produces the anti-cataplectic activity is unknown.

Therapeutic Recommendation

Sodium oxybate, or GHB, is a known drug of abuse. Abuse of this drug has been associated with death due to its CNS depressant effects. Reports of confusion, depression, and other neuropsychiatric events have occurred, even at recommended doses. As part of FDA approval, all patients and prescribers must enroll in a program designed to restrict distribution and provide postmarketing evaluations. Tricyclic antidepressants, such as imipramine, protriptyline, and clomipramine are currently used to control cataplectic attacks in narcoleptics. In clinical trials, sodium oxybate has been shown to reduce the number of cataplexy attacks, reduce daytime sleepiness in patients with narcolepsy, as well as decrease the frequency of inadvertent naps/sleep attacks and nighttime awakenings when compared to placebo. Approximately 80% of patients maintained concomitant stimulant use while taking sodium oxybate.

Dosing and Administration

Sodium oxybate is available as an oral solution that must be diluted with approximately 60 mL of water and must be taken nightly in two equal doses. It should be taken on an empty stomach and at a similar time each day. Both doses should be prepared prior to bedtime and administered while the patient is sitting up in bed due to the rapid onset of CNS depression. The recommended starting dose is 4.5 grams/night with the first dose given at bedtime after patient is in bed and the second dose 2.5-4 hours later.

The patient may need to set an alarm clock in order to wake up for the second dose. After two weeks, the prescriber should reassess the patient's symptoms. If they are not adequately controlled, the dose should be increased by no more than 1.5 grams/night and the patient should follow up in two weeks. If intolerable side effects occur, the nightly dosage should be decreased by 1.5 grams/night and the patient should follow up in two weeks. The maximum approved dosage is 9 grams/night.

Cost Comparison

Medication/Dose	Cost*		
	CVS	KMart	Rite Aid
Imipramine 100 mg/d	26.49	17.00	20.99
Clomipramine 150 mg/d	73.99	70.00	104.99
Protriptyline 20 mg/d	48.99	45.00	N/A
Fluoxetine 40 mg/d	142.99	151.99	148.99
Orphan Medical			
Sodium Oxybate 4.5 gm/d	369.90		
Sodium Oxybate 6 gm/d	493.20		
Sodium Oxybate 7.5 gm/d	616.50		
Sodium Oxybate 9 gm/d	739.80		

*Prices shown indicate a one month supply.
N/A = not available

Contraindications

Patients with hypersensitivity to sodium oxybate or any component of the formulation should not take this product. It is also contraindicated in patients who use ethanol or other CNS depressants, patients with semialdehyde dehydrogenase deficiency, hypertension, bradycardia related to cardiac disease, hypokalemia, epilepsy, or eclampsia.

Xyrem® Success Program

Sodium oxybate is made available to prescribers by contacting the centralized pharmacy through which the drug is dispensed (Orphan Medical). The pharmacy can be contacted at 1-877-67-XYREM and will send the prescriber educational materials about the risks and proper use of sodium oxybate. After the prescriber has read the materials and returned the necessary form, the pharmacy will send educational materials to the patient. After the patient has read the material, the drug can be shipped to the patient to begin therapy. The Xyrem® Success Program also includes patient surveillance via a post-marketing safety evaluation program and information to help minimize the risks of inadvertent use by others.

Special Populations

Geriatrics: There have been no studies of the pharmacokinetics of sodium oxybate in patients greater than the age of 65 years.

Pediatrics: There have been no studies of the pharmacokinetics of sodium oxybate in patients under the age of 18 years.

Gender: No differences were detected between male and female patients in the pharmacokinetics of sodium oxybate.

Race: There is insufficient data to evaluate any pharmacokinetic differences among races.

Renal insufficiency: No pharmacokinetic studies in patients have been performed in patients with renal dysfunction due to the fact that the kidney does not have a significant role in the excretion of sodium oxybate. There is not an expected alteration of pharmacokinetics in renal dysfunction.

Hepatic insufficiency: Sodium oxybate undergoes significant first-pass metabolism. AUC values in cirrhotic patients compared to healthy adults were doubled with apparent oral clearance halved. (In cirrhotic patients with ascites, elimination $t_{1/2}$ is approximately 59 minutes. It is approximately 32 minutes in cirrhotic patients without ascites vs. 22 min-

utes in healthy patients.) When starting a patient with hepatic insufficiency on sodium oxybate, the starting dose should be reduced by one-half and titrated carefully.

Drug Interactions

Coadministration of ethanol or other CNS depressants can result in potentiation of CNS depressant effects, thus is contraindicated with sodium oxybate. High-fat meals can decrease bioavailability, delay absorption, and decrease peak serum levels.

Adverse Effects

Adverse effects of sodium oxybate 6mg/day that occurred at a greater frequency (>1%) and at a higher rate than placebo include: asthenia (6 vs 3), infection (15 vs 3), viral infection (9 vs 3), pain (12 vs 6), diarrhea (6 vs 0), dyspepsia (9 vs 6), nausea (15 vs 6), vomiting (6 vs 0), myasthenia (3 vs 0), dizziness (30 vs 6), dream abnormalities (9 vs 0), hypertension (5 vs 3), sleep disorders (12 vs 3), diaphoresis (3 vs 0), and urinary incontinence (5 vs 0). Frequency of pain, nausea, vomiting, dizziness, and sleep disorders increased as daily dosage of sodium oxybate increased from 3mg, 6mg, and 9mg daily.

Pharmacology

Mechanism of Action: The exact mechanism of action by which sodium oxybate produces anti-cataplectic activity is not known; although it may be due to its interactions with several neurotransmitter pathways in the brain.

Absorption/Distribution: The bioavailability of sodium oxybate oral solution is ~25%. It is rapidly absorbed and peaks in 30-75 minutes. The volume of distribution ranges from 0.19-0.384 L/kg and it is less than 1% protein bound.

Metabolism/Excretion: Metabolism of sodium oxybate takes place primarily in the liver via the Krebs cycle to form water and carbon dioxide. Secondary metabolism occurs via beta oxidation. It is primarily excreted through the lungs as carbon dioxide with <5% excreted in the urine as unchanged drug.

Patient Information

1. Sodium oxybate is a controlled drug. It should only be used by the person for whom it was prescribed. It is illegal to share with others.
2. Keep in a safe place and prevent access by children or pets.
3. The medication will cause drowsiness quickly. Therefore, it must be taken at bedtime after getting in bed.
4. Sleepiness, dizziness, and confusion are possible side effects. These may carry over to the next day. Do not partake in activities requiring mental alertness until you know how this medication will affect you.
5. Do not take with food as this may decrease the amount of drug absorbed.
6. This drug may cause nausea, vomiting, or bedwetting. Notify your doctor if you experience breathing difficulties while asleep, abnormal thinking, depression, loss of consciousness, sleepwalking, or if you think that you may be pregnant.

References:

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3. Xyrem® NDA approval. July 17, 2002. <http://FDA.gov>.
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