Frovatriptan | apollo +9191 46 950

Frovatriptan

**CAS Number**: 158747-02-5

**Molecular Formula**: C_{14}H_{17}N_{3}O

**Molecular Weight**: 243.30 g/mol

**Systematic (IUPAC)**: (3R)-3-(methylamino)-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide

**Type**: small molecule

**Description**
Frovatriptan is a triptan drug developed by Vernalis for the treatment of migraine headaches, in particular those associated with menstruation. The product is licensed to Endo Pharmaceuticals in North America and Menarini in Europe. Frovatriptan causes vasoconstriction of arteries and veins that supply blood to the head. It is available as 2.5 mg tablets. Frovatriptan has mean terminal elimination half-life of approximately 26 hours, which is substantially longer than other triptans. Frovatriptan is available only by prescription in the United States, where a secondary New Drug Approval (sNDA) was filed in July 2006 and which is currently pending. The FDA anticipates completing its review of this application on or before the current PDUFA (Prescription Drug User Fee Act) review date of August 19, 2007. If the sNDA is approved, Frova® will be the only medication indicated in the U.S. for the short-term prevention of menstrual migraine (MM).

**Categories**
- Vasoconstrictor Agents
- Anti-inflammatory Agents
- Anti-migraine Agents
- Serotonin Agonists

**Taxonomy**

**Kingdom**: Organic

**Classes**
- Carbazoles
Tryptamines and Derivatives

**Substructures**
Indoles and Indole Derivatives
Aliphatic and Aryl Amines
Amino Ketones
Carbazoles
Pyrroles
Benzene and Derivatives
Carbamates and Derivatives
Heterocyclic compounds
Aromatic compounds
Carboxamides and Derivatives
Tryptamines and Derivatives
Imines
Benzoyl Derivatives
Carboxylic Acids and Derivatives
Cyclohexenes and Derivatives
Benzamides

**Pharmacology**

**Indication**: For the acute treatment of migraine attacks with or without aura in adults.

**Pharmacodynamics**: Frovatriptan is a second generation triptan 5-HT receptor agonist that binds with high affinity for 5-HT1B and 5-HT1D receptors. It is structurally distinct from, but pharmacologically related to other selective 5-HT1B/1D receptor agonists. Frovatriptan has no significant effects on GABAA mediated channel activity and has no significant affinity
for benzodiazepine binding sites. Frovatriptan is believed to act on extracerebral, intracranial arteries and to inhibit excessive dilation of these vessels in migraine. Research has shown that migraine can be caused by the swelling of blood vessels around the brain. Frovatriptan eases the pain associated with migraine by narrowing these blood vessels. Frovatriptan has one of the highest affinities for the 5-HT1B of the second-generation triptan agonists.

**Mechanism of action**: Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation; (2) direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem and (3) vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

**Absorption**: Frovatriptan is rapidly absorbed from the duodenum, but has low oral bioavailability.

Volume of distribution
- 4.2 L/kg [males]
- 3 L/kg [females]

**Protein binding**: Binding to serum proteins is low (approximately 15%). Reversible binding to blood cells at equilibrium is approximately 60%.

**Metabolism**: In vitro, cytochrome P450 1A2 appears to be the principal enzyme involved in the metabolism of
frovatriptan to several metabolites including hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan and desmethyl frovatriptan, and several other minor metabolites. Desmethyl frovatriptan has lower affinity for 5-HT1B/1D receptors compared to the parent compound. The N-acetyl desmethyl metabolite has no significant affinity for 5-HT receptors. The activity of the other metabolites is unknown.

**Route of elimination**: Radiolabeled compounds excreted in urine were unchanged frovatriptan, hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan and desmethyl frovatriptan, together with several other minor metabolites. Less than 10% of frovatriptan was excreted in urine after an oral dose.

**Half life**: 26 hours

**Clearance**
- 220 mL/min [male receiving IV dose of 0.8 mg]
- 130 mL/min [Female receiving IV dose of 0.8 mg]

**Toxicity**: There is no direct experience of any patient taking an overdose of Frovatriptan. The maximum single dose of frovatriptan given to male and female patients with migraine was 40 mg (16 times the clinical dose) and the maximum single dose given to healthy male subjects was 100 mg (40 times the clinical dose) without significant adverse events.

**Affected organisms**: Humans and other mammals
**Uses**
Frovatriptan is used to treat migraines. It helps to relieve headaches, pain and other symptoms of migraines, including sensitivity to light/sound, nausea, and vomiting. Prompt treatment allows you to get back to your normal routine and may decrease your need for other pain medications. Frovatriptan does not prevent future migraines or reduce how often you may get a headache. Frovatriptan belongs to a group of drugs called triptans. It affects a certain natural chemical (serotonin) that constricts blood vessels in the brain. It may also block other pain pathways in the brain.

**How To Use?**
Read the Patient Information Leaflet available from your pharmacist before you start using frovatriptan and each time you get a refill. Ask your doctor or pharmacist if you have any questions. Take this medication by mouth at the first sign of a migraine, or as directed by your doctor. It may be taken with or without food, although faster relief may occur when it is taken on an empty stomach. Do not take frovatriptan to prevent a migraine. If there is no improvement in your symptoms, do not take any more doses of this medication before talking to your doctor. If your symptoms are only partly relieved, or if your headache comes back, the U.S. manufacturer recommends that you may take a second dose after 2 hours, but take no more than 7.5 milligrams (3 doses) in a 24-hour period. The Canadian manufacturer recommends that you may take a second dose after 4 hours, but take no more than 5 milligrams (2 doses) in a 24-hour period. Follow your doctor's direction carefully. If you have any questions, be sure to ask your doctor or
pharmacist before you have to take this medication. If you have never taken this medication before and you have risk factors for heart disease (see Precautions), you may be advised to take your first dose in your doctor's office in order to monitor for rare but serious heart problems (e.g., heart attack). Your dosage is based on your medical condition and response to therapy. Tell your doctor if your condition does not improve or if it worsens.

**Drug Interactions**

See also Side Effects section. Your healthcare professionals (e.g., doctor or pharmacist) may already be aware of any possible drug interactions and may be monitoring you for it. Do not start, stop or change the dosage of any medicine before checking with them first. This drug should not be taken with the following medication because very serious interactions may occur: sibutramine. If you are currently using the medication listed above, tell your doctor or pharmacist before using frovatriptan. Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: certain types of antidepressants (e.g., SSRIs such as fluoxetine/paroxetine/sertraline, NSRIs such as venlafaxine). If you also take any ergotamine medication (e.g., dihydroergotamine or methysergide) or any other "triptan" drugs (e.g., zolmitriptan, rizatriptan), you will need to separate your frovatriptan dose from your dose of these other medications in order to lessen the chance of serious side effects. Ask your doctor how long you should wait between your doses of these drugs. Tell your doctor or pharmacist if you also take drugs that cause
drowsiness such as: certain antihistamines (e.g.,
diphenhydramine), anti-seizure drugs (e.g.,
carbamazepine), medicine for sleep or anxiety (e.g.,
alprazolam, diazepam, zolpidem), muscle relaxants,
narcotic pain relievers (e.g., codeine), psychiatric
medicines (e.g., chlorpromazine, amitriptyline,
risperidone, trazodone). Check the labels on all your
medicines (e.g., cough-and-cold products) because they
may contain drowsiness-causing ingredients. Ask your
pharmacist about the safe use of those products. This
document does not contain all possible interactions.
Therefore, before using this product, tell your doctor or
pharmacist of all the products you use. Keep a list of all
your medications with you, and share the list with your
doctor and pharmacist.

Why is this medication prescribed?
Frovatriptan is used to treat the symptoms of migraine
headaches (severe throbbing headaches that sometimes
are accompanied by nausea and sensitivity to sound and
light). Frovatriptan is in a class of medications called
selective serotonin receptor agonists. It works by
narrowing blood vessels in the brain. Frovatriptan does
not prevent migraine attacks.

How should this medicine be used?
Frovatriptan comes as a tablet to take by mouth. It is
usually taken at the first sign of a migraine attack. If
your symptoms improve after you take frovatriptan but
return after 2 hours or longer, you may take a second
tablet. However, if your symptoms do not improve after
you take frovatriptan, do not take a second tablet before
calling your doctor. Do not take more than three
frovatriptan tablets in any 24-hour period. Call your doctor if you need to take frovatriptan more than four times a month. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take frovatriptan exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.

You may take your first dose of frovatriptan in a doctor's office or other medical facility where you can be monitored for serious reactions.

Before taking frovatriptan, read the manufacturer's information for patients that comes with it.

**Other uses for this medicine**

This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

**What special precautions should I follow?**

Before taking frovatriptan:
- tell your doctor and pharmacist if you are allergic to frovatriptan or any other medications.
- do not take frovatriptan within 24 hours of another selective serotonin receptor agonist such as almotriptan (Axert), eletriptan (Relpax), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), or zolmitriptan (Zomig); or ergot-type medications such as bromocriptine (Parlodel), cabergoline (Dostinex), dihydroergotamine (D.H.E. 45, Migranal), ergoloid mesylates (Germinal, Hydergine), ergonovine (Ergotrate), ergotamine (Bellergal-S, Cafergot, Ergomar, Wigraine), methylergonovine (Methergine), methysergide (Sansert), and pergolide (Permax).
tell your doctor and pharmacist what other prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take. Be sure to mention any of the following: oral contraceptives (birth control pills); propranolol (Inderal); selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem, in Symbyax), fluvoxamine, paroxetine (Paxil), and sertraline (Zoloft); selective serotonin/norepinephrine reuptake inhibitors (SNRIs) such as duloxetine (Cymbalta), sibutramine (Meridia), and venlafaxine (Effexor). Your doctor may need to change the doses of your medications or monitor you carefully for side effects.

tell your doctor if you smoke, if you or any family members have or have ever had heart disease, if you have gone through menopause (change of life), and if you have or have ever had a heart attack; angina (chest pain); pounding heartbeat or shortness of breath; a stroke or 'mini-stroke'; high blood pressure; high cholesterol; diabetes; circulation problems such as varicose veins, blood clots in the legs, Raynaud's disease (problems with blood flow to the fingers, toes, ears, and nose) or ischemic bowel disease (bloody diarrhea and stomach pain caused by decreased blood flow to the intestines); or liver disease.

tell your doctor if you are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking frovatriptan, call your doctor.

you should know that frovatriptan may make you drowsy or dizzy. Do not drive a car or operate machinery until you know how this medication affects you.
talk to your doctor about your headache symptoms to make sure they are caused by migraine. Frovatriptan
should not be used to treat hemiplegic or basilar migraine or headaches caused by other conditions (such as cluster headaches).

**What special dietary instructions should I follow?**
Unless your doctor tells you otherwise, continue your normal diet.

**What side effects can this medication cause?**
Frovatriptan may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:
- dizziness
- headache
- dry mouth
- indigestion
- excessive tiredness
- flushing
- hot or cold feeling
- pain in joints or bones

Some side effects can be serious. The following symptoms are uncommon, but if you experience any of them, call your doctor immediately:
- tightness, pain, pressure, or heaviness in the chest, throat, neck, and/or jaw
- slow or difficult speech
- faintness
- weakness or numbness of an arm or leg
- severe stomach pain
- bloody diarrhea
- rapid, pounding, or irregular heartbeat
- difficulty breathing
- paleness or blue color of the fingers and toes
pain, burning, or tingling in the hands or feet
rash or itching
Frovatriptan may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.

What storage conditions are needed for this medicine?
Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom). Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

What other information should I know?
Keep all appointments with your doctor.
Do not let anyone else take your medication. Ask your pharmacist any questions you have about refilling your prescription.
It is important for you to keep a written list of all of the prescription and nonprescription (over-the-counter) medicines you are taking, as well as any products such as vitamins, minerals, or other dietary supplements. You should bring this list with you each time you visit a doctor or if you are admitted to a hospital. It is also important information to carry with you in case of emergencies.

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Frovatriptan

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