

# **Product Monograph**

**<sup>Pr</sup>JAMP FROVATRIPTAN**

**Frovatriptan Tablets**

**2.5 mg Frovatriptan (as Frovatriptan succinate monohydrate)**

**5-HT<sub>1</sub> Receptor Subtype Agonist**

**Migraine Therapy**

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#### **THERAPEUTIC CLASSIFICATION**

**Migraine Therapy**

#### **PHARMACOLOGICAL CLASSIFICATION**

**5-HT<sub>1</sub> Receptor Subtype Agonist**

#### **ACTIONS AND CLINICAL PHARMACOLOGY**

##### **Mechanism of Action**

JAMP FROVATRIPTAN (frovatriptan succinate) is a 5-HT receptor agonist that binds with high affinity for 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. Frovatriptan has no significant effects on GABA<sub>A</sub> 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.

##### **Pharmacokinetics**

Mean maximum blood concentrations (C<sub>max</sub>) in patients are achieved approximately 2 - 4 hours after administration of a single oral dose of frovatriptan 2.5 mg. The absolute bioavailability of

an oral dose of frovatriptan 2.5 mg in healthy subjects is about 20% in males and 30% in females. Food has no significant effect on the bioavailability of frovatriptan, but delays  $t_{\max}$  by one hour.

Binding of frovatriptan to serum proteins is low (approximately 15%). Reversible binding to blood cells at equilibrium is approximately 60%, resulting in a blood:plasma ratio of about 2:1 in both males and females. The mean steady state volume of distribution of frovatriptan following intravenous administration of 0.8 mg is 4.2 L/kg in males and 3.0 L/kg in females.

*In vitro*, cytochrome P450 1A2 appears to be the principal enzyme involved in the metabolism of frovatriptan. Following administration of a single dose of radiolabeled frovatriptan 2.5 mg to healthy male and female subjects, 32% of the dose was recovered in urine and 62% in feces.

Radiolabeled compounds excreted in the urine were unchanged frovatriptan, hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan and desmethyl frovatriptan, together with several other minor metabolites. Desmethyl frovatriptan has lower affinity for 5-HT<sub>1B/1D</sub> 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.

After an intravenous dose, mean clearance of frovatriptan was 220 and 130 mL/min in males and females, respectively. Renal clearance accounted for about 40% (82 mL/min) and 45% (60 mL/min) of total clearance in males and females, respectively. The mean terminal elimination half-life of frovatriptan in both males and females is approximately 26 hours.

The pharmacokinetics of frovatriptan are similar in migraine patients and healthy subjects.

### **Special Populations**

*Age:* Mean AUC of frovatriptan was 1.5 to 2-fold higher in healthy elderly subjects (age 65 - 77 years) compared to those in healthy younger subjects (age 21 - 37 years). There was no difference in  $t_{\max}$  or  $t_{1/2}$  between the two populations.

*Gender:* There was no difference in the mean terminal elimination half-life of frovatriptan in males and females. Bioavailability was higher, and systemic exposure to frovatriptan was approximately 2-fold greater, in females than males, irrespective of age.

*Renal Impairment:* Since less than 10% of frovatriptan succinate are excreted in urine after an oral dose, it is unlikely that the exposure to frovatriptan will be affected by renal impairment. The pharmacokinetics of frovatriptan following a single oral dose of 2.5 mg was not different in patients with renal impairment (5 males and 6 females, creatinine clearance 16 - 73 mL/min) and in subjects with normal renal function.

*Hepatic Impairment:* There is no clinical or pharmacokinetic experience with frovatriptan succinate in patients with severe hepatic impairment. The AUC in subjects with mild (Child-Pugh 5 - 6) to moderate (Child-Pugh 7 - 9) hepatic impairment is about twice as high as the AUC in young, healthy subjects, but within the range found among normal elderly subjects.

*Race:* The effect of race on the pharmacokinetics of frovatriptan has not been examined.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, blinded, balanced, two treatment, two period, two sequence, single dose, crossover comparative bioavailability study of JAMP FROVATRIPTAN (frovatriptan) 2.5 mg tablets (JAMP Pharma Corporation, Canada) and <sup>Pr</sup>Frova<sup>®/MD</sup> (frovatriptan) 2.5 mg tablets (Teva Canada Innovation), in 32 normal, healthy, adult, male and female human subjects under fasting conditions was conducted. The results from 31 subjects completing the study are summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Frovatriptan (1 x 2.5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test <sup>†</sup>	Reference <sup>*</sup>	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-72</sub> (ng.h/mL)	76.80 85.99 (49.27)	71.12 81.74 (56.20)	107.98	100.42 - 116.10
AUC <sub>I</sub> (ng.hr/mL)	85.54 96.14 (49.72)	80.29 92.42 (56.24)	106.54	98.96 - 114.70
C <sub>max</sub> (ng/mL)	5.47 5.73 (30.81)	5.28 5.62 (37.34)	103.59	97.05 - 110.57
T <sub>max</sub> <sup>§</sup> (h)	3.00 (2.00 - 5.00)	3.00 (2.00 - 5.00)		
T <sub>1/2</sub> <sup>€</sup> (h)	23.45 (21.25)	23.36 (23.42)		

<sup>†</sup> JAMP FROVATRIPTAN 2.5 mg tablets (JAMP Pharma Corporation)

<sup>\*</sup> <sup>Pr</sup>FROVA<sup>®/MD</sup> 2.5 mg frovatriptan tablets (Endo Pharmaceuticals Inc., USA; marketed by Teva Canada Innovation) was purchased in Canada.

<sup>§</sup> Expressed as median (range) only

<sup>€</sup> Expressed as the arithmetic mean (CV %) only

The efficacy of frovatriptan succinate in the acute treatment of migraine headaches was demonstrated in five randomized, double-blind, placebo-controlled, outpatient trials. Two of

these were dose-finding studies in which patients were randomized to receive doses of frovatriptan ranging from 0.5 – 40 mg. The three studies evaluating only one dose studied 2.5 mg. In these controlled short-term studies combined, patients were predominately female (88%) and Caucasian (94%) with a mean age of 42 years (range 18-69). Patients were instructed to treat a moderate or severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed for 24 hours after dosing.

The associated symptoms nausea, vomiting, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post-dose. In two of the trials a second dose of frovatriptan succinate was provided after the initial treatment, to treat recurrence of headache within 24 hours. Other medication, excluding other 5-HT<sub>1</sub> agonists and ergotamine-containing compounds was permitted from 2 hours after the first dose of Frovatriptan Tablets. The frequency and time to use of additional medications were also recorded.

In all five placebo-controlled trials, the percentage of patients achieving a headache response 2 and 4 hours after treatment was significantly greater for those taking frovatriptan succinate compared with those taking placebo (Table 1).

Lower doses of frovatriptan (1 mg or 0.5 mg) were not effective at 2 hours. Higher doses (5 mg to 40 mg) of frovatriptan showed no added benefit over 2.5 mg but did cause a greater incidence of adverse events.

**Table 1**  
**Percentage of Patients with Headache Response (Mild or No Headache) 2 and 4 Hours Following Treatment<sup>a</sup>**

Trial	Frovatriptan Succinate 2.5 mg		Placebo	
	2 hours	4 hours	2 hours	4 hours
1	42%* (n=90)	64%** (n=85)	22% (n=91)	38% (n=81)
2	38%* (n=121)	68%** (n=117)	25% (n=115)	33% (n=106)
3	39%* (n=187)	56%** (n=156)	21% (n=99)	31% (n=81)
4	46%** (n=672)	65%** (n=586)	27% (n=347)	38% (n=305)
5	37%** (n=438)	62%** (n=388)	23% (n=225)	32% (n=202)

<sup>a</sup> ITT observed data, excludes patients who had missing data or were asleep; \*0.001 ≤ p ≤ 0.050, \*\*p < 0.001 in comparison with placebo

**Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because trials are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of the response may be expected to vary considerably from study to study.**

In patients with migraine-associated nausea, photophobia and phonophobia at baseline there was a decreased incidence of these symptoms in frovatriptan succinate treated patients compared to placebo.

Following the treatment of migraine with frovatriptan succinate in controlled clinical trials, there was low recurrence of migraine headaches (7% - 25%). This is postulated to be due to the long half-life of frovatriptan.

Efficacy was unaffected by a history of aura; gender; age; or concomitant medications commonly used by migraine patients.

## **INDICATIONS AND CLINICAL USE**

Jamp Frovatriptan (frovatriptan succinate) is indicated for the acute treatment of migraine attacks with or without aura in adults.

Jamp Frovatriptan is not intended for the prophylactic therapy of migraine or for the use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see **CONTRAINDICATIONS**). The safety and effectiveness of frovatriptan succinate have not been established for cluster headache, which is present in an older, predominantly male, population.

## **CONTRAINDICATIONS**

**Jamp Frovatriptan (frovatriptan succinate) is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardia). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive Jamp Frovatriptan. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospasm forms of angina such as the Prinzmetal's variant, all forms of myocardial infarction, and silent myocardial ischemia). Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral**



**vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).**

**Because Jamp Frovatriptan may increase blood pressure, it is contraindicated in patients with severe or uncontrolled hypertension (see WARNINGS).**

**Jamp Frovatriptan is contraindicated within 24 hours of treatment with another 5-HT<sub>1</sub> agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.**

**Jamp Frovatriptan is contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine.**

**Because there are no data available, Jamp Frovatriptan is contraindicated in patients with severe hepatic impairment.**

**Jamp Frovatriptan is contraindicated in patients who are hypersensitive to frovatriptan or any of the inactive ingredients in the tablets.**

## **WARNINGS**

**Jamp Frovatriptan (frovatriptan succinate) should only be used where a clear diagnosis of migraine has been established.**

**Risk of Myocardial Ischemia and/or Infarction and other Adverse Cardiac Events: frovatriptan succinate has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT<sub>1</sub> agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT<sub>1</sub> agonists, and may therefore also occur with Jamp Frovatriptan.**

**Because of the potential of this class of compounds (5-HT<sub>1B/1D</sub> agonists) to cause coronary vasospasm, Jamp Frovatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT<sub>1</sub> agonists (including Jamp Frovatriptan) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors such as: hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age, unless a cardiovascular examination provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical**

history, electrocardiogram (ECG) or other evaluations reveal findings indicative of, or consistent with, coronary artery vasospasm, or myocardial ischemia, Jamp Frovatriptan should not be administered (see CONTRAINDICATIONS).

These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events, such as myocardial infarction or coronary ischemia have occurred in patients without evidence of underlying cardiovascular disease.

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of Jamp Frovatriptan take place in a clinical setting, such as the physician's office or a similarly staffed medical facility, unless the patient has previously received frovatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately following the first use of Jamp Frovatriptan in a patient with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

If symptoms consistent with angina occur after the use of Jamp Frovatriptan, ECG evaluation should be carried out to look for ischemic changes.

**It is recommended that patients who are intermittent long-term users of Jamp Frovatriptan and who have or acquire risk factors predictive of CAD as described above undergo periodic interval cardiovascular evaluation as they continue to use Jamp Frovatriptan.**

**The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease are inadvertently exposed to Jamp Frovatriptan.**

**Cardiac Events and Fatalities with 5-HT<sub>1</sub> Agonists:** Serious adverse cardiac events including acute myocardial infarction, life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of 5-HT<sub>1</sub> agonists. Considering the extent of use of 5-HT<sub>1</sub> agonists in patients with migraine, the incidence of these events is extremely low.

**Premarketing Experience with Frovatriptan:** Among more than 3000 patients with migraine who participated in premarketing clinical trials of frovatriptan succinate, no deaths or serious cardiac events were reported which were related to the use of frovatriptan succinate.

**Post-marketing experience with Frovatriptan:** Rare reports of serious cardiovascular events have been reported in association with the use of frovatriptan succinate, this includes chest tightness and tachycardia. There have been rare reports of serious allergic type reactions, including anaphylactic reactions. The uncontrolled nature of post-marketing surveillance, however, makes it impossible to definitely determine the proportion of the reported cases that were actually caused by frovatriptan or to reliably assess causation in individual cases.

**Cerebrovascular Events and Fatalities with 5-HT<sub>1</sub> Agonists:** Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with other 5-HT<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with Jamp Frovatriptan in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should be noted, however, that patients who suffer from migraine may have an increased risk of certain cerebrovascular events such as stroke, hemorrhage or transient ischemic attack.

**Special Cardiovascular Pharmacology Studies With Another 5-HT<sub>1</sub> Agonist:**

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT<sub>1</sub> agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT<sub>1</sub> agonist is not known.

Similar studies have not been done with frovatriptan succinate. However, owing to the common pharmacodynamic actions of 5-HT<sub>1</sub> agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

**Hypersensitivity:** Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred in patients receiving other 5-HT<sub>1</sub> agonists. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, Jamp Frovatriptan should not be used in patients having a history of hypersensitivity to chemically-related 5-HT<sub>1</sub> receptor agonists. (see **ADVERSE REACTIONS** and **PRECAUTIONS**).

### **Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome**

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors

(SNRIs) and triptans. If concomitant treatment with Jamp Frovatriptan and SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or SNRIs (e.g., venlafaxine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see **PRECAUTIONS, Drug Interactions**).

**Other Vasospasm-Related Events:** 5-HT<sub>1</sub> agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT<sub>1</sub> agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

**Effects on Blood Pressure:** Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT<sub>1</sub> agonists. In young healthy subjects, there were statistically significant increases in systolic and diastolic blood pressure only at single doses of 80 mg frovatriptan (32 times the clinical dose) and above. These increases were transient, resolved spontaneously and were not clinically significant. Jamp Frovatriptan is contraindicated in patients with severe or uncontrolled hypertension (see **CONTRAINDICATIONS**). In patients with controlled hypertension, Jamp Frovatriptan should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

## **PRECAUTIONS**

### **General:**

Jamp Frovatriptan (frovatriptan succinate) should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see **ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations**).

For a given attack, if a patient has no response to the first dose of Jamp Frovatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

**Medication Overuse Headache:** Overuse of acute migraine treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients.

Withdrawal of the treatment may be necessary.

**Cardiovascular:** Discomfort in the chest, neck, throat and jaw (including pain, tightness, pressure and heaviness) have been reported after treatment with frovatriptan succinate. Because 5-HT<sub>1</sub> agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients



who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following Jamp Frovatriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see **CONTRAINDICATIONS** and **WARNINGS**).

**Neurologic Conditions:** Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT<sub>1</sub> agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of Jamp Frovatriptan.

**Seizures:** Caution should be observed if Jamp Frovatriptan is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.

**Hepatically Impaired Patients:** Since there is no clinical or pharmacokinetic experience with frovatriptan succinate in patients with severe hepatic impairment it is contraindicated in this population (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**). Jamp Frovatriptan can be used in patients with mild to moderate hepatic impairment (see **ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations**).

**Binding to Melanin-Containing Tissues:** When pigmented rats were given a single oral dose of 5 mg/kg of radiolabelled frovatriptan, the radioactivity in the eye after 28 days was 87% of the value measured after 8 hours. This suggests that frovatriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that frovatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with frovatriptan were noted in toxicity studies. Although no systemic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmological monitoring are made, prescribers should be aware of the possibility of long-term ophthalmologic effects.

#### **Carcinogenicity:**

The carcinogenic potential of frovatriptan was evaluated in an 84-week study in mice (4, 13 and 40 mg/kg/day), a 104-week study in rats (8.5, 27 and 85 mg/kg/day), and a 26-week study in p53(+/-) transgenic mice (20, 62.5, 200, and 400 mg/kg/day). Although the maximum tolerated dose (MTD) was not achieved in the 84-week mouse study and in female rats, exposures at the highest doses studied were many fold greater than those achieved at the maximum recommended daily human dose (MRHD) of 7.5 mg. There were no increases in tumor incidence in the 84-week mouse study at doses producing 140 times the exposure achieved at the MRHD based on blood AUC comparisons. In the rat study, there was a statistically significant increase in the incidence of pituitary adenomas in males only at 85 mg/kg/day, a dose that produced 250 times the exposure achieved at the MRHD based on AUC comparisons. In the 26-week p53 (+/-) transgenic mouse study, there was an increased incidence of subcutaneous sarcomas in females dosed at 200 and 400 mg/kg/day, or 390 and 630 times the human exposure based on AUC

comparisons. The incidence of sarcomas was not increased at lower doses that achieved exposure 180 and 60 times the human exposure. These sarcomas were physically associated with subcutaneously implanted animal identification transponders. There were no other increases in tumor incidence of any type in any dose group. The relevance of these sarcomas to humans is unknown.

### **Mutagenicity:**

Frovatriptan was clastogenic in human lymphocyte cultures, in the absence of metabolic activation. In the bacterial reverse mutation assay (Ames test), frovatriptan produced an equivocal response in the absence of metabolic activation. No mutagenic or clastogenic activity were seen in an *in vitro* mouse lymphoma assay, an *in vivo* mouse bone marrow micronucleus test, or an *ex vivo* assay for unscheduled DNA synthesis in rat liver.

### **Impairment of Fertility:**

Male and female rats were dosed prior to and during mating, and up to implantation, at doses of 100, 500, and 1000 mg/kg/day (equivalent to approximately 130, 650 and 1300 times the MRHD on a mg/m<sup>2</sup> basis). At all dose levels, there was an increase in the number of females that mated on the first day of pairing compared to control animals. This occurred in conjunction with a prolongation of the estrous cycle. In addition females had a decreased mean number of corpora lutea, and consequently a lower number of live fetuses per litter, which suggested a partial impairment of ovulation. There were no other fertility-related effects.

When pregnant rats were administered frovatriptan during the period of organogenesis at oral doses of 100, 500 and 1000 mg/kg/day (equivalent to 130, 650 and 1300 times the MRHD) on a mg/m<sup>2</sup> basis) there were dose related increases in incidences of both litters and total numbers of fetuses with dilated ureters, unilateral and bilateral pelvic cavitation, hydronephrosis, and hydroureters. A no-effect dose for renal effects was not established. This signifies a syndrome of related effects on a specific organ in the developing embryo in all treated groups, which is consistent with a slight delay in fetal maturation. This delay was also indicated by a treatment related increased incidence of incomplete ossification of the sternebrae, skull and nasal bones in all treated groups. Slightly lower fetal weights and an increased incidence of early embryonic deaths in treated rats were observed; although not statistically significant compared to control, the latter effect occurred in both the embryo-fetal developmental study and in the prenatal-postnatal developmental study. There was no evidence of this latter effect at the lowest dose level studied, 100 mg/kg/day (equivalent to 130 times the MRHD on a mg/m<sup>2</sup> basis). When pregnant rabbits were dosed throughout organogenesis at doses up to 80 mg/kg/day (equivalent to 210 times the MRHD on a mg/m<sup>2</sup> basis) no effects on fetal development were observed.

**Use in the Elderly:** Mean blood concentrations of frovatriptan in elderly subjects were 1.5- to 2-times higher than those seen in younger adults (see **PHARMACOLOGY, Special Populations**). Because migraine occurs infrequently in the elderly, clinical experience with frovatriptan succinate are limited in such patients.

**Pediatric Use:** Safety and effectiveness of frovatriptan succinate in pediatric patients have not been established; therefore, Jamp Frovatriptan is not recommended for use in patients under 18 years of age.

Post-marketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

**Nursing Mothers:** It is not known whether frovatriptan is excreted in human milk. Frovatriptan and/or its metabolites are excreted in the milk of lactating rats with the maximum concentration being four-fold higher than that seen in blood. Therefore, caution should be exercised when considering the administration of Jamp Frovatriptan to a nursing woman.

**Pregnancy:** There are no adequate and well-controlled trials in pregnant women. Jamp Frovatriptan should be used during pregnancy only if clearly needed.

**Dependence Liability:** Although the abuse potential of frovatriptan succinate have not been specifically assessed in clinical trials, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received frovatriptan succinate. The 5-HT<sub>1</sub> agonists, as a class, have not been associated with drug abuse.

**Drug Interactions:** Frovatriptan is not an inhibitor of human monoamine oxidase (MAO) enzymes or cytochrome P450 (isozymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4) *in vitro* at concentrations up to 250 to 500-fold higher than the highest blood concentrations observed in man at a dose of 2.5 mg. No induction of drug metabolizing enzymes was observed following multiple dosing of frovatriptan to rats or on addition to human hepatocytes *in vitro*. Although no

clinical studies have been performed, it is unlikely that frovatriptan will affect the metabolism of co-administered drugs metabolized by these mechanisms.

**Oral Contraceptives:** Retrospective analysis of pharmacokinetic data from females across trials indicated that the mean  $C_{\max}$  and AUC of frovatriptan are 30% higher in those subjects taking oral contraceptives compared to those not taking oral contraceptives. The effect of frovatriptan succinate on the pharmacokinetics of oral contraceptives has not been studied.

**Ergotamine and Ergot-Containing Drugs:** The AUC and  $C_{\max}$  of frovatriptan (2 x 2.5 mg dose) were reduced by approximately 25% when co-administered with ergotamine tartrate.

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Due to a theoretical risk of a pharmacodynamic interaction, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and Jamp Frovatriptan within 24 hours of each other is contraindicated (see **CONTRAINDICATIONS**).

#### **Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors**

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see **WARNINGS**).

**Propranolol:** Propranolol increased the AUC of frovatriptan 2.5 mg in males by 60% and in females by 29%. The  $C_{\max}$  of frovatriptan was increased 23% in males and 16% in females in

the presence of propranolol. The  $t_{\max}$  as well as half-life of frovatriptan, though slightly longer in the females, were not affected by concomitant administration of propranolol.

**Moclobemide:** The pharmacokinetic profile of frovatriptan was unaffected when a single oral dose of frovatriptan 2.5 mg was administered to healthy female subjects receiving the MAO-A inhibitor, moclobemide, at an oral dose of 150 mg bid for 8 days.

**Other 5-HT<sub>1</sub> Agonists:** The administration of frovatriptan succinate with other 5-HT<sub>1</sub> agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of Jamp Frovatriptan and other 5-HT<sub>1</sub> agonists within 24 hours of each other is contraindicated (see **CONTRAINDICATIONS**).

**Laboratory Tests:** Frovatriptan succinate are not known to interfere with commonly employed clinical laboratory tests. No specific laboratory tests are recommended for monitoring patients prior to and/or after the treatment with Jamp Frovatriptan.

**Information to be provided to the Patient:** Physicians should instruct their patients to read the patient package insert before taking Jamp Frovatriptan. See the section entitled **CONSUMER INFORMATION** included in this Product Monograph.

## ADVERSE REACTIONS

**Serious cardiac events, including some that have been fatal, have occurred following the use of other 5-HT<sub>1</sub> agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).**

**Incidence in Controlled Clinical Trials:** Among 1554 patients treated with frovatriptan succinate in four placebo-controlled studies (Trials 1, 3, 4 and 5 in Table 1), only 1% (16) of the patients withdrew because of the treatment-emergent adverse events. In a long- term, open-label study where patients were allowed to treat multiple migraine attacks with frovatriptan succinate for up to 1 year, 5% (26/496) patients discontinued due to treatment-emergent adverse events.

The treatment-emergent adverse events that occurred most frequently following the administration of frovatriptan 2.5 mg (i.e., in at least 1% of patients), and at an incidence  $\geq 1\%$  greater than with the placebo, in the four placebo-controlled trials, were dizziness, paresthesia, headache, dry mouth, fatigue, flushing, hot or cold sensation, chest pain, dyspepsia, dysesthesia, throat-tightness and skeletal pain.



Table 2 lists treatment-emergent adverse events reported within 48 hours of drug administration that occurred with frovatriptan 2.5 mg at an incidence rate of  $\geq 1\%$  and more than 1% more often than placebo, in the first attack in four placebo-controlled trials (Trials 1, 3, 4 and 5 in Table 1). These studies involved 2392 patients (1554 frovatriptan 2.5 mg and 838 placebo). The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these incidence estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

**Table 2**  
**Treatment-Emergent Adverse Events (Incidence  $\geq 1\%$  and 1% Greater Than Placebo) of**  
**Patients in Four Placebo-Controlled Migraine Trials**

<b>Adverse Events</b>	<b>Frovatriptan 2.5 mg</b> (n=1554)	<b>Frovatriptan 5 mg</b> (n=99)	<b>Placebo</b> (n=838)
<i>Symptoms of Potentially Cardiac Origin</i>			
Chest Pain	2%	3%	1%
Throat tightness	2%	1%	0%
<i>Central &amp; peripheral nervous system</i>			
Dizziness	8%	NR	5%
Headache	4%	NR	3%
Paresthesia	4%	NR	2%
Hypertonia	NR	4%	0%
<i>Gastrointestinal system disorders</i>			
Mouth dry	3%	NR	1%
Dyspepsia	2%	3%	1%
<i>Body as a whole - general disorders</i>			
Fatigue	5%	4%	2%
Asthenia	NR	4%	1%
Hot or cold sensation*	3%	NR	2%
Rigors	NR	2%	1%
Dysesthesia	1%	NR	0%
<i>Respiratory system disorders</i>			
Rhinitis	NR	3%	1%
<i>Psychiatric disorders</i>			
Euphoria	NR	2%	0%
<i>Musculo-skeletal</i>			
Skeletal pain	3%	NR	2%
<i>Vascular</i>			
Flushing	4%	NR	2%

\*The term “sensation” encompasses adverse events described as pain, discomfort, pressure, constriction, numbness and tingling.

NR: No incidence rates of  $\geq 1\%$  and 1% greater than placebo.

Frovatriptan succinate is generally well tolerated. The incidence of adverse events in clinical trials did not increase when up to 2 doses were used within 24 hours. The majority of adverse events were mild or moderate and transient. The incidence of adverse events in four placebo-controlled clinical trials was not affected by gender, age or concomitant medications commonly used by migraine patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

**Other Events Observed in Association with frovatriptan succinate:** In the paragraphs that follow, the incidence of less commonly reported adverse events in four placebo-controlled trials are presented. The incidence of each adverse event is calculated as the number of patients reporting the event at least once divided by the number of patients who used frovatriptan succinate. All adverse events reported within 48 hours of drug administration in the first attack in four placebo-controlled trials involving 2392 patients (1554 frovatriptan 2.5 mg and 838 placebo) are included, except those already listed in Table 2, those too general to be informative, those not reasonably associated with the use of the drug and those which occurred at the same or a greater incidence in the placebo group. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events are those occurring in between 1/100 and 1/1000 patients, and rare adverse events are those occurring in fewer than 1/1000 patients.

*Central and peripheral nervous system:* Frequent: dysesthesia and hypoesthesia. Infrequent: tremor, hyperesthesia, migraine aggravated, involuntary muscle contractions, vertigo, ataxia,

abnormal gait and speech disorder. Rare: hypertonia, hypotonia, abnormal reflexes and tongue paralysis.

*Gastrointestinal:* Frequent: vomiting, abdominal pain and diarrhea. Infrequent: dysphagia, flatulence, constipation, anorexia, esophagospasm and increased salivation. Rare: change in bowel habits, cheilitis, eructation, gastroesophageal reflux, hiccup, peptic ulcer, salivary gland pain, stomatitis and toothache.

*Body as a whole:* Frequent: pain. Infrequent: asthenia, rigors, fever, hot flashes and malaise. Rare: feeling of relaxation, leg pain and edema mouth.

*Psychiatric:* Frequent: insomnia and anxiety. Infrequent: confusion, nervousness, agitation, euphoria, impaired concentration, depression, emotional lability, amnesia, thinking abnormal and depersonalization. Rare: depression aggravated, abnormal dreaming and personality disorder.

*Musculoskeletal:* Infrequent: myalgia, back pain, arthralgia, arthrosis, leg cramps and muscle weakness.

*Respiratory:* Frequent: sinusitis and rhinitis. Infrequent: pharyngitis, dyspnea, hyperventilation and laryngitis.

*Vision disorders:* Frequent: abnormal vision. Infrequent: eye pain, conjunctivitis and abnormal lacrimation.

*Skin and appendages:* Frequent: sweating increased. Infrequent: pruritus, and bullous eruption.

*Hearing and vestibular disorders:* Frequent: tinnitus. Infrequent: ear ache, and hyperacusis.

*Heart rate and rhythm:* Frequent: palpitation. Infrequent: tachycardia. Rare: bradycardia.

*Metabolic and nutritional disorders:* Infrequent: thirst and dehydration. Rare: hypocalcemia and hypoglycemia.

*Special senses, other disorders:* Infrequent: taste perversion.

*Urinary system disorders:* Infrequent: micturition frequency and polyuria. Rare: nocturia, renal pain and abnormal urine.

*Cardiovascular disorders, general:* Infrequent: abnormal ECG.

*Platelet, bleeding and clotting disorders:* Infrequent: epistaxis. Rare: purpura.

*Autonomic nervous system:* Rare: syncope.

**Long Term Safety:**

The adverse events which occurred within 48 hours of drug administration in a long-term open-label safety study were similar to those that occurred in the placebo-controlled trials. The most frequent adverse events were: nausea, dizziness, fatigue, somnolence, headache, dyspepsia, skeletal pain, flushing and paresthesia.

**Post-marketing experience with Frovatriptan:** Rare reports of serious cardiovascular events have been reported in association with the use of frovatriptan succinate, this includes chest tightness and tachycardia. There have been rare reports of serious allergic type reactions, including anaphylactic reactions. The uncontrolled nature of post-marketing surveillance, however, makes it impossible to definitely determine the proportion of the reported cases that were actually caused by frovatriptan or to reliably assess causation in individual cases.

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There is no direct experience of any patient taking an overdose of frovatriptan succinate. 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.

As with other 5-HT<sub>1</sub> receptor agonists, there is no specific antidote for frovatriptan. The elimination half-life of frovatriptan is 26 hours, therefore if overdose occurs, the patient should be monitored closely for at least 48 hours and be given any necessary symptomatic treatment. The effects of hemo- or peritoneal dialysis on blood concentrations of frovatriptan are unknown.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **DOSAGE AND ADMINISTRATION**

### **Adults:**

The recommended dosage of Jamp Frovatriptan (frovatriptan succinate) is a single tablet (frovatriptan 2.5 mg) taken orally with fluids for migraine headache with or without aura. Jamp Frovatriptan is recommended only for the acute treatment of migraine attacks, and should not be used prophylactically.

If the headache recurs after initial relief, a second dose may be taken between 4 and 24 hours after the first dose. The total daily dose of Jamp Frovatriptan should not exceed 2 tablets (2 x 2.5 mg per day).

There is no evidence that a second dose of frovatriptan is effective in patients who do not respond to a first dose of the drug for the same headache.

Jamp Frovatriptan is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) due to the absence of clinical data.

Jamp Frovatriptan is contraindicated in patients with uncontrolled or severe hypertension. In patients with mild to moderate controlled hypertension, patients should be treated cautiously.

The safety of treating an average of more than 4 migraine attacks in a 30 day period has not been established.



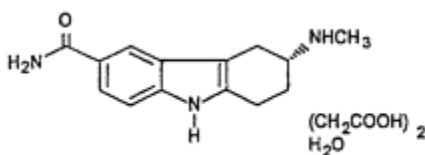
## PHARMACEUTICAL INFORMATION

### Drug Substance:

*Common Name:* Frovatriptan succinate monohydrate

*Chemical Name:* (+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole monosuccinate monohydrate

*Structural Formula:*



*Molecular formula:* C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O.C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>.H<sub>2</sub>O

*Molecular Weight:* 379.4 g/mol

*Description:* Frovatriptan monosuccinate monohydrate is water-soluble, i.e., its aqueous solubility is more than 100 mg/mL at pH 3 or above. It has a melting range of 165°-172°C. The pKa value is 10.38. It is not hygroscopic. No evidence of polymorphism has been detected.

**Composition:** Each Jamp Frovatriptan (frovatriptan succinate monohydrate) tablet for oral administration contains 3.91 mg frovatriptan succinate monohydrate, equivalent to 2.5 mg of Frovatriptan (as Frovatriptan succinate monohydrate). Each tablet also contains the inactive ingredients silicon dioxide USP, lactose anhydrous Ph.Eur, magnesium stearate Ph.Eur, microcrystalline cellulose Ph.Eur, Sodium Starch Glycolate Ph.Eur, macrogol 3350 Ph.Eur, Lactose Monohydrate Ph.Eur, titanium dioxide Ph.Eur, Hypromellose Ph.Eur and triacetin Ph.Eur .

**Stability and Storage Recommendations:** Store at controlled room temperature (15°C - 30°C).

### **AVAILABILITY OF DOSAGE FORMS**

Jamp Frovatriptan (frovatriptan succinate monohydrate) tablets, containing 2.5 mg of frovatriptan (as frovatriptan succinate monohydrate), are available as round, white to off white, film-coated tablets. The tablets are available in blister cards of 6 tablets, 1 blister card per carton.

## PHARMACOLOGY

### Nonclinical Studies:

Nonclinical pharmacology studies of frovatriptan investigated its primary activity as well as general activity (i.e., safety). The primary vasoconstrictor activity was examined in several *in vitro* studies with human and other mammalian arteries and in the cat and dog *in vivo*. The safety pharmacology was examined using *in vivo* models that included the mouse, cat, and dog.

The primary activity studies show that frovatriptan is a potent vasoconstrictor in isolated cerebral arteries, as well as a potent, but low efficacy, vasoconstrictor in isolated coronary arteries. By virtue of its apparent partial agonist activity in human isolated coronary arteries, frovatriptan demonstrates a functional selectivity for cerebral arteries over coronary arteries. In cell-based assays *in vitro*, frovatriptan is a potent, full agonist at human recombinant 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors and a moderately potent, partial agonist at 5-HT<sub>1F</sub> receptors. Unlike sumatriptan, frovatriptan is a moderately potent, full agonist at 5-HT<sub>7</sub> receptors. The desmethyl metabolite of frovatriptan (SB 205555-A) exhibits affinity for 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, 5-HT<sub>1F</sub> and 5-HT<sub>7</sub> binding sites with pKi values approximately 0.5 units lower than those for frovatriptan, whereas the N-acetyl desmethyl metabolite (SB 210199) exhibits no significant affinity at these sites.

In terms of general pharmacological effects, frovatriptan is a consistent and potent constrictor of the carotid vascular bed in the cat and dog *in vivo*. It is devoid of pronounced or dose-related

gross behavioral effects in the mouse. Frovatriptan attenuates carrageenan-induced thermal hyperalgesia but does not possess anti-nociceptive activity in the mouse.

Administration of frovatriptan IV or intra-arterially (coronary artery) as a bolus at high doses to anesthetized dogs (3 studies) or cats (1 study), does not consistently affect systemic blood pressure. A modest transient decrease was evoked in the cat, whereas a slight, transient increase was evoked in 1 study in the dog. At the highest doses, heart rate was slightly increased in the cat but was unaltered in 2 studies in the dog. IV doses of up to 2 mg/kg had no effect on any ECG parameter in the dog. A transient hyperpnea was noted during and immediately after IV administration in 1 experiment in the dog. Coronary blood flow and vascular resistance were unaltered. Thus, no adverse effect on cardiac or respiratory function was observed at a range of bolus IV dose levels substantially greater than those which will occur in clinical use.

## **TOXICOLOGY**

### **Acute and Long-term Studies:**

Single dose toxicity studies in rats and mice indicate that frovatriptan has low acute oral toxicity with a lethal dose in excess of 2000 mg/kg. Toxicity studies with frovatriptan up to the maximum tolerated dose in several species give no indication of adverse effects (including mutagenic or carcinogenic effects) likely to be relevant to the proposed clinical use of frovatriptan.

In rodents, repeat dose oral studies in mice, demonstrated a no-observed-adverse-effect-level of 40 mg/kg/day for 84 weeks, giving a 140- to 400-fold safety margin based upon human exposure

(AUC) to frovatriptan in blood at the proposed dose of 2.5 mg (0.04 mg/kg). Repeat dose oral studies in rats, demonstrated a no-observed-adverse-effect-level of 10 mg/kg/day for 26 weeks, giving a 30- to 50-fold safety margin based upon human exposure to frovatriptan in blood at the proposed dose of 2.5 mg (0.04 mg/kg). Effects that were observed in rats included peripheral vasodilation as well as renal, adrenal and thyroid histopathological lesions. These effects, which only occurred at high doses are not considered to be relevant to man at the proposed clinical dose.

In dogs, repeat dose oral studies demonstrated no histopathological changes attributable to frovatriptan administration at blood exposures up to 130-fold higher than those anticipated in man. Dose levels were limited by the pharmacological effects of frovatriptan on the central nervous and cardiovascular systems. No evidence of any ocular toxicity has been noted in long term oral studies at blood exposures 50- to 130-fold higher than those anticipated in man.

Tachycardia, a compensatory response to peripheral vasodilatation and a consequence of the pharmacological effects of frovatriptan, was observed in dogs but is not anticipated to be a problem with the much lower dose levels used clinically.

## BIBLIOGRAPHY

1. Buchan P, Keywood C, Ward C. Pharmacokinetics of frovatriptan (VML 251.SB209509) in male and female subjects. *Headache* 1998; 13:177.
2. Buchan P, Keywood C, Ward C. Pharmacokinetics of frovatriptan (VML 251.SB209509) in male and female subjects. *European Journal of Neurology* 1998; 5:S58.
3. Goldstein J, Elkind A, Keywood C, Klapper J, Ryan R. A low-dose range finding study of frovatriptan: a potent selective 5-HT<sub>[1B/1D]</sub> agonist for the acute treatment of migraine. *Headache* 1998; 38:382.
4. Goldstein J, Elkind A, Keywood C, Klapper J, Ryan R. A low-dose range finding study of frovatriptan: a potent selective 5-HT<sub>[1D]</sub> agonist for the acute treatment of migraine. *Cephalalgia* 1998; 18:53.
5. Goldstein J, Keywood C. A study of the efficacy and safety of low doses of frovatriptan (VML 251), a potent selective 5-HT<sub>[1B/1D]</sub> agonist for the acute treatment of migraine. *European Journal of Neurology* 1998; 5:S46.
6. Keywood C. Effects of ascending doses of frovatriptan (VML 251) on the cardiovascular system of healthy volunteers. *Functional Neurology* 1998; 13:178.
7. Keywood C. The effects of ascending doses of oral frovatriptan (VML 251/SB209509), a potent selective 5-HT<sub>[1B/1D]</sub> agonist for the acute treatment of migraine on the cardiovascular system of healthy male volunteers. *Headache* 1998; 38:388.

8. Ryan R and Keywood C. A preliminary study of frovatriptan (VML 251), a potent cerebroselective 5-hydroxytryptamine (5-HT)<sub>[1B/1D]</sub> agonist for the acute treatment of migraine. *European Journal of Neurology* 1998; 5:S46.
9. Ryan R and Keywood C. A preliminary study of VML 251 (SB209509) a novel 5HT<sub>[1B/1D]</sub> agonist for the treatment of acute migraine. *Cephalalgia* 1997; 17:418.
10. Cole P, Rabasseda X. Frovatriptan: a selective type 1B/1D serotonin receptor agonist for the treatment of migraine headache. *Drugs Today (Barc)* 2002 Sept;38(9):615-29.
11. Goldstein J. Frovatriptan: a review. *Expert Opin Pharmacother* 2003; Jan;4(1):83-93.
12. Rapoport AM. Frovatriptan: pharmacological differences and clinical results. *Curr Med Res Opin* 2001;17 Suppl 1:S68-70.
13. Tepper SJ, Rapoport AM, Sheftell FD. Mechanisms of action of the 5-HT<sub>1B/1D</sub> receptor agonists. *Arch Neurol* 2002 Jul;59(7):1084-8.
14. Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002 Apr;42 Suppl 2:S93-9.
15. Ryan R, Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. *Headache* 2002 Apr;42 Suppl 2:S84-92.
16. Rapoport A, Ryan R, Goldstein J, Keywood C. Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache* 2002 Apr;42 Suppl 2:S74-83.
17. Buchan P, Wade A, Ward C, Oliver SD, Stewart AJ, Freestone S. Frovatriptan: a review of drug-drug interactions. *Headache* 2002 Apr;42 Suppl 2:S63-73.

18. Buchan P, Keywood C, Wade A, Ward C. Clinical pharmacokinetics of frovatriptan. Headache 2002 Apr;42 Suppl 2:S54-62.
19. Comer MB. Pharmacology of the selective 5-HT (1B/1D) agonist frovatriptan. Headache 2002 Apr;42 Suppl 2:S47-53.
20. Goldstein J, Keywood C. 251/96/14 Study Group. Frovatriptan for the acute treatment of migraine: a dose-finding study. Headache 2002 Jan;42(1):41-8.
21. PRODUCT MONOGRAPH of <sup>Pr</sup> FROVA<sup>®/MD</sup> frovatriptan succinate tablets, frovatriptan 2.5 mg; Endo Pharmaceuticals Inc., Distributed by: Teva Canada Limited, Toronto, Ontario, M1B 2K9; Marketed by: Teva Canada Innovation, Montreal, Quebec, H2Z 1S8, Canada; Date of Revision: December 17, 2012.



**PART III: CONSUMER INFORMATION**

**PrJAMP FROVATRIPTAN**  
**Frovatriptan Tablets**  
**2.5 mg Frovatriptan (as frovatriptan succinate monohydrate)**

This leaflet is part III of a three-part “Product Monograph” published when Jamp Frovatriptan was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FROVA. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start taking FROVA. Also, read the insert each time you renew your prescription, just in case anything has changed. Remember, this insert does not take the place of careful discussions with your doctor. You and your doctor should discuss Jamp Frovatriptan when you start taking your medication and at regular checkups.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

Jamp Frovatriptan is a medication used for the treatment of migraine attacks in adults. Jamp Frovatriptan is a member of a class of drugs called 5-HT<sub>1</sub> agonists.

**What it does:**

Migraine headache is believed to be caused by a widening of the blood vessels in the head. Jamp Frovatriptan narrows the vessels and relieves the pain and other symptoms of migraine headache.

**When it should not be used:**

Jamp Frovatriptan should only be taken if you have a migraine headache. Jamp Frovatriptan should not be used continuously to prevent or reduce the number of attacks. Do not use Jamp Frovatriptan to treat other types of headaches that might be caused by other conditions.

Please tell your doctor all of your symptoms. Your doctor will decide whether you have migraines and if Jamp Frovatriptan is for you.

**Do not take Jamp Frovatriptan if you:**

- have uncontrolled high blood pressure
- have heart disease or history of heart disease, irregular heart beat, angina
- have had a stroke, transient ischemic attacks (TIAs)
- have circulation (blood flow) problems, Raynaud’s syndrome

- have any allergic reaction to frovatriptan or to any other ingredients in Jamp Frovatriptan (see “What the non-medicinal ingredients are”)
- have a severe liver problem
- are pregnant, think you might be pregnant, are trying to become pregnant or are using inadequate contraception, unless you have discussed this with your doctor.

**What the medicinal ingredient is:**

frovatriptan succinate monohydrate

**What the non-medicinal ingredients are:**

Silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, Opadry II white.

Opadry II white includes Macrogol 3350, titanium dioxide, Hypromellose, Lactose monohydrate and triacetin.

**What dosage forms it comes in:**

Tablets: 2.5 mg frovatriptan

**WARNINGS AND PRECAUTIONS**

BEFORE you use Jamp Frovatriptan talk to your doctor if you:

- have a history of high blood pressure, chest pain, shortness of breath, strokes, or heart disease
- have any risk factors for heart disease including high blood pressure, diabetes, high cholesterol, obesity, smoking,
- a family history of heart disease; are postmenopausal or a male over 40 years of age
- plan to take any drugs without a prescription, and/or those you normally take for a migraine; or herbal supplements
- have any past or present medical problems
- have previous allergies to any medication
- have irregular heartbeats
- have angina
- are over 65 years of age
- have liver and/or kidney disease
- have epilepsy or seizures
- experience numbness on one side of your body when you have a headache
- experience a headache different from your usual migraine headache attack
- are pregnant, or planning to become pregnant
- are breast-feeding or plan to breast-feed
- are using inadequate contraception. Tell your doctor if you take propranolol.

Ask your physician for instructions about taking Jamp

## IMPORTANT: PLEASE READ

Frovatriptan if you are taking selective serotonin reuptake inhibitors (SSRIs) such as sertraline, escitalopram and fluoxetine or serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine or duloxetine for depression. A life-threatening condition called serotonin syndrome can happen when medicines called triptans, such as FROVA, and medicines used to treat depression and mood disorders called SSRIs or SNRIs are used together. Signs and symptoms of serotonin syndrome include the following: restlessness, diarrhea, hallucinations, coma, loss of coordination, nausea, fast heart beat, vomiting, increased body temperature, changes in blood pressure and overactive reflexes.

If you use Jamp Frovatriptan too often, it may make your headaches worse. If this happens, your doctor may tell you to stop taking FROVA.

### INTERACTIONS WITH THIS MEDICATION

#### Do not take Jamp Frovatriptan if you:

- have taken another similar drug (a serotonin receptor agonist) within the last 24 hours of treatment, e.g., sumatriptan (Imitrex<sup>®</sup>), naratriptan (Amerge<sup>®</sup>), zolmitriptan (Zomig<sup>®</sup>), almotriptan (Axert<sup>®</sup>), rizatriptan (Maxalt<sup>™</sup>) or eletriptan (Relpax<sup>®</sup>) unless your doctor tells you it is safe to do so.
- have taken ergotamine type medications such as ergotamine (Bellergal<sup>®</sup>- Spacetabs<sup>®</sup>, Cafegot<sup>®</sup>, Ergomar<sup>®</sup>, Gravergol<sup>®</sup>, Megral<sup>®</sup>), dihydroergotamine (Dihydroergotamine (DHE), or Migranal<sup>®</sup>), or methysergide (Sansert<sup>®</sup>) within the last 24 hours unless your doctor tells you it is safe to do so.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Take one Jamp Frovatriptan tablet with fluid for your migraine headache. If your headache comes back after the initial dose, a second tablet may be taken not sooner than 4 hours after the first dose.

If your headache is not relieved by the first tablet, do not take the second tablet for the same attack without first consulting your doctor. Do not take more than 2 tablets (2 x 2.5 mg) a day. If your condition worsens, seek medical attention.

#### Overdose:

If you think you have taken too much Jamp Frovatriptan, contact your healthcare professional,

hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If anyone other than you accidentally takes your tablets they should seek medical advice immediately.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all prescription drugs, Jamp Frovatriptan can cause side effects. The most common side effects associated with the use of Jamp Frovatriptan are:

- dizziness
- fatigue (tiredness)
- headache (other than a migraine headache)
- paresthesia (feeling of tingling).

If you feel dizziness or fatigue you should take extra care, do not drive or operate machinery.

Less common side effects associated with Jamp Frovatriptan are:

- flushing (redness of the skin lasting a short time)
- sensation of temperature change (feeling hot or cold)
- dry mouth
- dyspepsia
- dysesthesia (impairment of touch sensation)
- skeletal pain.

If you experience any of the above symptoms, tell your doctor at your next appointment.

In very rare cases, patients taking this class of medicines experience serious heart problems, stroke, or increased blood pressure.

If you develop pain, tightness, heaviness, or pressure in your chest, throat, neck, or jaw contact your doctor right away.

Also tell your doctor if you experience symptoms that suggest an allergic reaction such as a rash or itching, or if any of the above symptoms persist or worsen.

## IMPORTANT: PLEASE READ

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
Sensations of numbness, tingling, feeling hot or cold, pain	√		
Sensations of pain, pressure or tightness in the chest or throat			√
Very Rare			
Serious heart problems (stroke, or increased blood pressure, pain, tightness, heaviness, or pressure in your chest, throat, neck or jaw)			√
Allergic Reactions (rash or itching)			√

*This is not a complete list of side effects. For any unexpected effects while taking Jamp Frovatriptan, contact your doctor or pharmacist.*

### HOW TO STORE IT

Keep your Jamp Frovatriptan tablets in their packaging in a safe place out of reach of children. They may be harmful to children.

Store at controlled room temperature (15°C - 30°C). Do not use after the expiry date. If your doctor decides to stop your treatment do not keep any left over tablets. You should take all expired or unused medicines to your pharmacy for safe disposal. Medicine should not be flushed down a toilet as it is not environmentally friendly.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice*

### MORE INFORMATION

If you want more information about JAMP Frovatriptan:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or by calling the sponsor at: 1-866-399-9091

This leaflet was prepared by  
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