

Product Monograph

Pr FROVA[®]

frovatriptan succinate tablets

frovatriptan 2.5 mg

5-HT₁ Receptor Subtype Agonist

Migraine Therapy

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frovatriptan 2.5 mg

THERAPEUTIC CLASSIFICATION

Migraine Therapy

PHARMACOLOGICAL CLASSIFICATION

5-HT₁ Receptor Subtype Agonist

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

FROVA[®] (frovatriptan succinate) is a 5-HT receptor agonist that binds with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Frovatriptan has no significant effects on GABA_A 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_{max}) 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_{1B/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.

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 FROVA[®] is 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 FROVA[®] 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 STUDIES

The efficacy of FROVA[®] (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 FROVA[®] was provided after the initial treatment, to treat recurrence of headache within 24 hours. Other medication, excluding other 5-HT₁ agonists and ergotamine-containing compounds was permitted from 2 hours after the first dose of FROVA[®]. 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 FROVA[®] 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^a

Trial	FROVA [®] (frovatriptan 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)

^a 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 FROVA[®] treated patients compared to placebo.

Following the treatment of migraine with FROVA[®] tablets 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

FROVA[®] (frovatriptan succinate) is indicated for the acute treatment of migraine attacks with or without aura in adults.

FROVA[®] 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 FROVA[®] have not been established for cluster headache, which is present in an older, predominantly male, population.

CONTRAINDICATIONS

FROVA[®] (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 FROVA[®]. 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 FROVA[®] may increase blood pressure, it is contraindicated in patients with severe or uncontrolled hypertension (see WARNINGS).

FROVA[®] is contraindicated within 24 hours of treatment with another 5-HT₁ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

FROVA[®] is contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine.

Because there are no data available, FROVA[®] is contraindicated in patients with severe hepatic impairment.

FROVA[®] is contraindicated in patients who are hypersensitive to frovatriptan or any of the inactive ingredients in the tablets.

WARNINGS

FROVA[®] (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:

FROVA[®] has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT₁ 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-HT₁ agonists, and may therefore also occur with FROVA[®].

Because of the potential of this class of compounds (5-HT_{1B/1D} agonists) to cause coronary vasospasm, FROVA[®] should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT₁ agonists (including FROVA[®]) 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, FROVA[®] 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 FROVA[®] 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 FROVA[®] 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 FROVA[®], ECG evaluation should be carried out to look for ischemic changes.

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

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease are inadvertently exposed to FROVA[®].

Cardiac Events and Fatalities with 5-HT₁ 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-HT₁ agonists. Considering the extent of use of 5-HT₁ 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 FROVA[®], no deaths or serious cardiac events were reported which were related to the use of FROVA[®].

Post-marketing experience with Frovatriptan: Rare reports of serious cardiovascular events have been reported in association with the use of FROVA[®], 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-HT₁ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with other 5-HT₁ 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 FROVA 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-HT₁ Agonist:

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT₁ 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-HT₁ agonist is not known.

Similar studies have not been done with FROVA[®]. However, owing to the common pharmacodynamic actions of 5-HT₁ 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-HT₁ 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, FROVA[®] should not be used in patients having a history of hypersensitivity to chemically-related 5-HT₁ 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 FROVA 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-HT₁ agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT₁ 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-HT₁ 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. FROVA[®] is contraindicated in patients with severe or uncontrolled hypertension (see **CONTRAINDICATIONS**). In patients with controlled hypertension, FROVA 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-HT₁ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General:

FROVA[®] (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 FROVA[®], the diagnosis of migraine should be reconsidered before administration of a second dose.

Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, tightness, pressure and heaviness) have been reported after treatment with FROVA[®]. Because 5-HT₁ 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 FROVA[®] 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-HT₁ 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 FROVA[®].

Seizures: Caution should be observed if FROVA[®] 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 FROVA[®] in patients with severe hepatic impairment it is contraindicated in this population (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**). FROVA[®] 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/m² 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/m² 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/m² 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/m² 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 FROVA[®] is limited in such patients.

Pediatric Use: Safety and effectiveness of FROVA[®] in pediatric patients have not been established; therefore, FROVA[®] 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 FROVA[®] to a nursing woman.

Pregnancy: There are no adequate and well-controlled trials in pregnant women. FROVA[®] should be used during pregnancy only if clearly needed.

Dependence Liability: Although the abuse potential of FROVA[®] has not been specifically assessed in clinical trials, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received FROVA[®]. The 5-HT₁ 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 FROVA[®] 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 FROVA[®] 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-HT₁ Agonists: The administration of FROVA[®] with other 5-HT₁ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of FROVA[®] and other 5-HT₁ agonists within 24 hours of each other is contraindicated (see **CONTRAINDICATIONS**).

Laboratory Tests: FROVA[®] is 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 FROVA[®].

Information to be provided to the Patient: Physicians should instruct their patients to read the patient package insert before taking FROVA[®]. See the section entitled **INFORMATION FOR THE PATIENT** included in this Product Monograph.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of other 5-HT₁ 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 FROVA[®] (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 FROVA[®] 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

Adverse Events	Frovatriptan 2.5 mg (n=1554)	Frovatriptan 5 mg (n=99)	Placebo (n=838)
<i>Symptoms of Potentially Cardiac Origin</i>			
Chest Pain	2%	3%	1%
Throat tightness	2%	1%	0%
<i>Central & 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.

FROVA[®] 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 FROVA[®]: 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 FROVA[®]. 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 FROVA[®], 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 FROVA[®] (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-HT₁ 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.

DOSAGE AND ADMINISTRATION

Adults:

The recommended dosage of FROVA[®] (frovatriptan succinate) is a single 2.5 mg tablet taken orally with fluids for migraine headache with or without aura. FROVA[®] 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 FROVA[®] 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.

FROVA[®] is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) due to the absence of clinical data.

FROVA[®] 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.

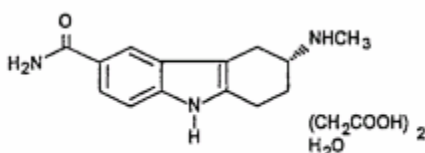
PHARMACEUTICAL INFORMATION

Drug Substance:

Common Name: Frovatriptan succinate

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

Structural Formula:



Molecular formula: C₁₄H₁₇N₃O.C₄H₆O₄.H₂O

Molecular Weight: 379.4

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 9.93. It is not hygroscopic. No evidence of polymorphism has been detected.

Composition: Each FROVA[®] (frovatriptan succinate) tablet for oral administration contains 3.91 mg frovatriptan succinate, equivalent to 2.5 mg of frovatriptan. Each tablet also contains the inactive ingredients lactose NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, sodium starch glycollate NF, magnesium stearate NF, hydroxypropylmethylcellulose USP, polyethylene glycol 3000 USP, triacetin USP, and titanium dioxide dye USP.

Stability and Storage Recommendations: Store at controlled room temperature, 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F). Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

FROVA[®] (frovatriptan succinate) tablets, containing 2.5 mg of frovatriptan (base) as the succinate, are available as round, white, film-coated tablets debossed with 2.5 on one side and “E” on the other side. The tablets are available in blister cards of 7 tablets, 1 blister card per carton.

INFORMATION FOR THE PATIENT

Please read this information before you start taking FROVA[®] (frovatriptan succinate) tablets. 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 FROVA[®] when you start taking your medication and at regular checkups.

What is FROVA[®] and what is it used for?

FROVA[®] is a medication used for the treatment of migraine attacks in adults. FROVA[®] should not be used continuously to prevent or reduce the number of attacks. It is a member of a class of drugs called selective serotonin receptor agonists. It should only be taken if you have a migraine headache. Do not use FROVA[®] to treat headaches that might be caused by other conditions.

FROVA[®] tablets can only be obtained on prescription from a doctor. Please tell your doctor all of your symptoms. Your doctor will decide whether you have migraines and if FROVA[®] is for you.

You will find more information about migraine at the end of this insert.

How should you take FROVA[®]?

Take one FROVA[®] 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.

Who should not take FROVA®?

Do not take FROVA® 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 the tablet
- have severe liver problem.

Can I take FROVA® with any other medication?

Do not take FROVA® if you:

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

(DHE), or Migranal[®]), or methysergide (Sansert[®]) within the last 24 hours unless your doctor tells you it is safe to do so.

What you should tell your doctor before and during treatment with FROVA[®]?

Please tell your doctor if you:

- are pregnant, or planning to become pregnant
- are breast-feeding or plan to breast-feed
- 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
 - Postmenopausal
 - male over 40 years of age
 - or plan to take any drugs without a prescription, herbal supplements and those you normally take for a migraine.
- 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 kidney disease
- have epilepsy or seizures
- experience numbness on one side of your body when you have headache
- headache different from your usual migraine headache attacks
- are using inadequate contraception.

Tell your doctor if you take

- Propranolol
- selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine), Luvox (fluvoxamine), Paxil (paroxetine), and Zoloft (sertraline), or serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (EFFEXOR® XR), two types of drugs for depression or other disorders.

These medicines may affect how FROVA® works, or FROVA® may affect how these medicines work.

Use during pregnancy

Do not use FROVA® if you 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 are the possible side effects of FROVA®?

Like all prescription drugs, FROVA® can cause side effects. The most common side effects associated with the use of FROVA® 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 FROVA® 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) and 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.

What should I do if I take too many FROVA[®] tablets?

If you take more medication than you have been told to take, you should contact your doctor, hospital emergency department, or nearest poison control center immediately, even if you do not feel sick.

What is a migraine and how does it differ from other headaches?

Migraine is an intense, throbbing that often affects one side of the head. It often includes nausea, vomiting, and sensitivity to light and sound. The pain and symptoms from a migraine headache may be worse than the pain and symptoms of a common headache. Migraine headaches usually last for hours or longer.

Some people may have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

Only your doctor can determine that your headache is a migraine headache, so it is important that you discuss all of your symptoms with your doctor.

How does FROVA[®] work during a migraine attack?

Migraine headache is believed to be caused by a widening of the blood vessels in the head.

FROVA[®] narrows the vessels and relieves the pain and other symptoms of migraine headache.

What dosage form does FROVA® come in?

FROVA® tablets are available as round, white, film-coated tablets debossed with 2.5 on one side and “E” on the other side. The tablets are available in blister cards of 7 tablets, 1 blister card per carton.

How should I store my FROVA® tablets?

Keep your tablets in their packaging in a safe place where children cannot reach them. They may be harmful to children. Store your tablets at a temperature above 15°C (59°F) and below 30°C (86°F). Protect them from moisture. Do not store or use your FROVA® tablets beyond the expiry date printed on the back of the pack. If your doctor decides to stop your treatment, do not keep any left over tablets.

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

Where should I go for further information?

If you have any questions or concerns about FROVA® or migraine, talk to your doctor or pharmacist.

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_{1B} and 5-HT_{1D} receptors and a moderately potent, partial agonist at 5-HT_{1F} receptors. Unlike sumatriptan, frovatriptan is a moderately potent, full agonist at 5-HT₇ receptors. The desmethyl metabolite of frovatriptan (SB 205555-A) exhibits affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F} and 5-HT₇ binding sites with pK_i 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.

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