

PRODUCT MONOGRAPH

^{Pr}SANDOMIGRAN & ^{Pr}SANDOMIGRAN DS

Pizotifen hydrogen malate

0.5 mg and 1 mg Pizotifen Tablets

THERAPEUTIC CLASSIFICATION

Serotonin and Tryptamine Antagonist

Migraine Prophylaxis

ATC code: N02CX

Paladin Labs Inc.
6111 Royalmount Avenue, Suite 102
Montreal, Quebec
H4P 2T4
Control No.: 152247

Date of revision:
October 30, 2012

NAME OF DRUG

PrSANDOMIGRAN & PrSANDOMIGRAN DS

(pizotifen tablets as hydrogen malate)

THERAPEUTIC CLASSIFICATION

Serotonin and Tryptamine Antagonist

Migraine Prophylaxis

ACTION

Sandomigran (pizotifen as hydrogen malate) is a strong serotonin and tryptamine antagonist, with weak anticholinergic, anti-histaminic and anti-kinin effects. It also possesses sedative and appetite-stimulating properties.

The mode of action of Sandomigran in preventing migraine is not fully understood but it is known to inhibit the permeability increasing effect of serotonin and histamine to control the transudation of plasmakinin across cranial vessel membranes, an effect which may alter pain thresholds. Sandomigran also inhibits serotonin re-uptake by blood platelets, impacting tonicity and decreasing passive distension of extracranial arteries.

INDICATIONS AND CLINICAL USE

Sandomigran (pizotifen as hydrogen malate) may be used for the prophylactic management of migraine.

In various clinical trials, about 1/3 to 2/3 of patients with migraine experienced some benefit from Sandomigran and in most trials it was more effective than placebo in reducing the frequency or severity of attacks.

Sandomigran is not useful for the clinical treatment of acute migrainous attack or for the treatment of tension headaches.

CONTRAINDICATIONS

Sandomigran (pizotifen as hydrogen malate) is contraindicated for patients:

- taking monoamine oxidase (MAO) inhibitors,
- with pyloroduodenal obstruction and stenosing pyloric ulcer,
- who are hypersensitive to pizotifen or to any ingredient in the formulation or component of the container (for a complete listing, see the **Dosage Forms** section of the product monograph),
- in children under the age of 12.

WARNINGS AND PRECAUTIONS

Renal impairment

Caution is required in patients with renal impairment. Dosage adjustment may be necessary.

Hepatic impairment

Caution is required in patients with hepatic impairment. Dosage adjustment may be necessary.

After prolonged use, hepatotoxic effects might occur and patients should be advised to report for adequate laboratory evaluation. Hepatic injury has been reported, ranging from transaminase elevations to severe hepatitis. Pizotifen treatment should be discontinued if there is any clinical

evidence of hepatic dysfunction during treatment and until the cause of the liver abnormality is determined.

Withdrawal symptoms

Acute withdrawal reactions have been reported following abrupt cessation of pizotifen, therefore, gradual withdrawal is recommended. Withdrawal symptoms include depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder, loss of consciousness, anorexia and rapid weight loss (see **ADVERSE REACTIONS**).

Dependence/Tolerance

Some patients developed tolerance to Sandomigran with prolonged use of the drug. Increase in dosage, not exceeding the maximum recommended daily dose, may overcome this tolerance.

Effects on the ability to drive and use machines

Patients should be warned that Sandomigran may cause dizziness, somnolence, fatigue, sedation and other CNS effects. Therefore, caution should be exercised when driving or using machines. Patients being treated with Sandomigran and presenting with somnolence, dizziness and/or fatigue episodes must be instructed to refrain from engaging in activities where impaired alertness may put themselves or others at risk.

Anticholinergic effects

In view of the weak anticholinergic effect of Sandomigran, caution is required in patients with narrow-angle glaucoma or with a predisposition to urinary retention (e.g., prostatic hypertrophy). In general, patients with narrow-angle glaucoma should not be given drugs with possible anticholinergic effects, unless they are required and the patient is under special care and medical supervision for this condition.

Effects on Weight

Sandomigran treatment leads to weight gain in a significant number of patients and may be associated with excessive weight loss upon discontinuation. Caution is advised in patients who are vulnerable to excess weight gain or weight loss.

Lactose

Sandomigran coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, lactase deficiency, sucrose-isomaltase insufficiency or glucose-galactose malabsorption should not take Sandomigran.

Visual Impairments

A limited number of cases of lens opacities have been reported but did not appear to be drug-related. Pizotifen use has also been associated with ocular dysfunctions including increased intraocular pressure, pupil dilation and diplopia. It is recommended that any impairment in vision be reported to the attending physician for further investigation.

Special Populations

Patients with diabetes or cardiovascular disease should be given Sandomigran with caution, and appropriate laboratory tests should be done at regular intervals.

Pregnant Women

The safety of Sandomigran for use during human pregnancy has not been established. Sandomigran should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

Animal studies show that pizotifen enters the milk.

Although the concentrations of pizotifen measured in the milk of treated mothers are not likely to affect the infant, its use in nursing mothers is not recommended.

Pediatrics (<12 years of age)

Sandomigran is contraindicated in children under the age of 12 (see **CONTRAINDICATIONS**).

Adolescents (12-17 years of age)

There is limited evidence supporting the safety and efficacy of Sandomigran in children 12-17 years of age, therefore Sandomigran should be used with caution in this age group.

Epilepsy

Seizures as undesirable effects have been observed more frequently in patients with epilepsy. Sandomigran should be used with caution in patients with epilepsy.

ADVERSE REACTIONS

Increased appetite, weight gain and drowsiness (including somnolence and fatigue) are the most common side effects. Physicians should be aware of the potential negative effects of Sandomigran (pizotifen as hydrogen malate) in special populations already with an excess in weight or in normal weight population where an excess in weight could be deleterious (arterial hypertension, diabetes mellitus and hypercholesterolemia). A gradual increase in the dosage of Sandomigran is recommended to minimize or reduce the incidence of drowsiness.

Table 1 is based on pizotifen post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported by the estimated number of patients exposed to the drug during the same time period. The causal relationship between pizotifen and the emergence of these events has not been established.

Table 1: Pizotifen Post-Market Spontaneous Adverse Event Reports

Adverse Event	Reported Frequency				
	Very Common ≥10%	Common ≥1%	Un- common <1% and ≥0.1%	Rare <0.1% and ≥0.01%	Very Rare <0.01%
Gastrointestinal disorders:					
Nausea		X			
Dry mouth		X			
Constipation			X		
General disorders and administration site conditions					
Fatigue		X			
Immune system disorders					
Hypersensitivity reactions				X	
Face edema				X	
Urticaria				X	
Rash				X	
Metabolism and nutrition disorders					
Appetite stimulating effect and increase in body weight	X				
Musculoskeletal and connective tissue disorders					
Myalgia				X	
Arthralgia				X	
Nervous system disorders					
Somnolence		X			
Dizziness		X			
Paresthesia				X	
Seizures					X
Psychiatric disorders					
Depression				X	
CNS stimulation (e.g. aggression, agitation) in children				X	
Hallucination				X	
Insomnia				X	
Anxiety				X	
Sleep disorder				X	

Sandomigran use has also been associated with ocular dysfunctions including increased IOP (intraocular pressure), pupil dilation and diplopia.

Acute withdrawal reactions have been reported following abrupt cessation of pizotifen, therefore, gradual withdrawal is recommended. Withdrawal symptoms include anxiety, tremors, insomnia, nausea, and loss of consciousness. Anorexia and rapid weight loss have also been observed.

The following adverse reactions have also been identified during post-approval use of Sandomigran:

Hepatobiliary disorders: Fulminant hepatitis, Hepatic enzyme increased, Hepatitis, Jaundice.

Musculoskeletal and connective tissue disorders: Muscle cramps.

Nervous system disorders: Sedation.

Reproductive system and breast disorders: amenorrhoea, breast enlargement, breast pain, nonpuerperal lactation.

DRUG INTERACTIONS

Pizotifen is extensively metabolized in the liver, primarily by N-glucuronidation. Increased plasma concentration of pizotifen upon concomitant administration of drugs which exclusively undergo glucuronidation cannot be excluded.

Central Nervous System (CNS) agents: Central effects of sedatives, hypnotics, antihistamines, including certain common cold preparations, alcohol, psychotherapeutic agents or other drugs with CNS depressant effects may be enhanced. Tolerance to alcohol may be reduced.

Antihypertensives: Sandomigran (pizotifen) may reduce the efficacy of antihypertensive medications (adrenergic neurone blockers) as it antagonizes their hypotensive effect. Patient blood pressure monitoring is therefore recommended.

Monoamine Oxidase Inhibitors: MAOIs can prolong and intensify the anticholinergic effects of antihistaminic substances. Concomitant use with MAOIs should therefore be avoided (see **CONTRAINDICATIONS**).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Adults

The symptoms of overdose in adults are sedation, drowsiness, dizziness, hypotension, dryness of the mouth, confusion, tachycardia, ataxia, nausea, vomiting, dyspnea, cyanosis, convulsions, coma, respiratory paralysis and CNS depression. Drowsiness precedes excitement, convulsions and postictal depression.

Children

Antihistamine poisoning in children exhibits excitation, hallucinations, ataxia, incoordination, convulsions, fixed dilated pupils, flushed faces, and fever (pyrexia), leading to coma and cardiorespiratory collapse.

Treatment

Administration of activated charcoal is recommended. In case of very recent uptake, if vomiting has not occurred spontaneously, induce emesis or perform gastric lavage and diuresis. Supportive measures should be instituted to maintain respiration and vital signs should be monitored; severe hypotension must be corrected (*caveat*: adrenaline (epinephrine) may produce paradoxical effects).

Because Sandomigran can cause tachycardia, an ECG should be performed and attention directed at the QRS and QT intervals. Patients with abnormal ECGs or signs of evolving toxicity should undergo ECG monitoring.

Short-acting barbiturates or benzodiazepines (diazepam or lorazepam) may be used for the treatment of excitatory states or convulsions. Analeptics (i.e., stimulating the central nervous system, the respiratory system or the cardiovascular system) should be avoided.

DOSAGE AND ADMINISTRATION

Adults

Oral treatment should be initiated with a dose of 0.5 mg at bedtime. This is increased gradually to a total dose of 1.5 mg administered at bedtime or in three divided doses. The dosage range is 1 to 6 mg/day. Up to 3mg may be given as a single dose. The average maintenance dose is 1.5 mg/day.

Geriatrics (>65 years of age):

The safety and efficacy of Sandomigran (pizotifen) in patients 65 years of age or older have not been established. Caution should be exercised with the use of Sandomigran in the elderly, recognizing the more frequent hepatic, renal, central nervous system and cardiovascular dysfunctions, and more frequent use of concomitant medications in this population.

Pediatrics (<12 years of age)

Sandomigran is contraindicated in children under the age of 12.

Adolescents (12-17 years of age)

Sandomigran may be prescribed in adolescents over the age of 12 years. Oral treatment should be initiated with a dose of 0.5 mg at bedtime. A maximum single dose of 1mg can be given at night. Daily doses up to a maximum of 1.5 mg may be given in divided doses.

Dosing Considerations:

Since migraine is a paroxysmal but basically chronic disorder, treatment must extend over an adequate period of time in order to obtain maximal benefit. While some patients have responded rather quickly, a 4-week trial period should be instituted to determine the true efficacy of Sandomigran in specific cases. The periodic nature of the disorder will have to be considered in determining when and for how long therapy should be maintained.

Since some investigators have observed a change in headache pattern after several months of therapy, a drug-free interval is advisable to reassess the necessity of continuing treatment. The dosage should be reduced gradually during the last 2 weeks of each treatment course to avoid a "headache rebound".

As with other antiserotonin agents, the benefits of Sandomigran decrease after a period of time in a certain number of patients.

STORAGE AND STABILITY

Store at room temperature (15-30°C) and protect from exposure to light and moisture. Keep in a safe place out of the sight and reach of children.

DOSAGE FORMS

Sandomigran:

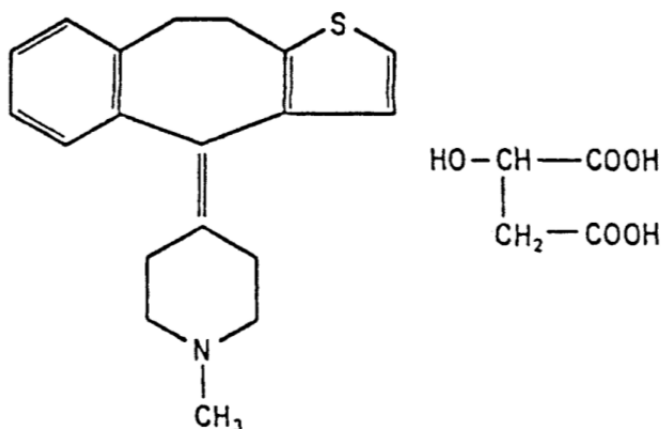
Each ivory, sugar-coated tablet contains: 0.5 mg of pizotifen (as hydrogen malate), lactose monohydrate, corn starch, povidone, magnesium stearate, propyl-paraben, acacia, colloidal silicone dioxide, cetyl palmitate, sugar and talc. Available in bottles of 100 and 500.

Sandomigran DS:

Each whitish with bevelled edge, scored on one side tablet contains: 1 mg of pizotifen (as hydrogen malate), lactose anhydrous, magnesium stearate, and microcrystalline cellulose. Available in bottles of 100.

CHEMISTRY AND PHARMACOLOGY

Pizotifen is a white to yellowish crystalline powder, readily soluble in water and organic solvents, and is designated chemically as 4-(9,10-Dihydro-4H-benzo[4,5]cycloheptal [1,2-b]thien-4-ylidene)-1-methylpiperidine hydrogen malate. It has the following structural formula:



A variety of *in vitro* and *in vivo* laboratory investigations indicated antagonistic or blocking actions of pizotifen towards serotonin and histamine and relatively weak anticholinergic activity. Pizotifen had very little effect as an epinephrine or bradykinin antagonist.

Tests for potentiation of barbiturate anesthesia and inhibition of locomotion in the mouse indicated that pizotifen had weak sedative properties. However, pizotifen was found to be more active in rats than either imipramine or amitriptyline in the antagonism of tetrabenazine-induced depression.

Pizotifen given orally (40 mg/kg), subcutaneously (5 mg/kg) and intravenously (1.25 mg/kg) to male Rhesus monkeys produced slight sedation, but no change in cardiac or respiratory rates during the subsequent four hours.

Pizotifen given intravenously (i.v.; 1 to 10 mg/kg) rapidly produced hypotension in dogs; reversion to normal pressures occurred within 30 minutes. Immediate increased heart rates were produced by the maximal dose but they quickly subsided. Blood pressure response to adrenaline was enhanced (2 mg/kg i.v.).

Blood sugar studies of normal and alloxan-treated rats did not indicate any hypoglycemic effects of pizotifen.

Pharmacokinetics:

Absorption

Absorption half-life of pizotifen in man by the gastro-intestinal tract is 0.5 to 0.8 hours and nearly complete (80%). The absolute bioavailability is 78%. Maximum blood levels are reached 5 hours after oral administration.

Metabolism

Pizotifen is highly metabolised. Metabolism is mostly achieved through glucuronidation, and the main metabolite, N-glucuronide conjugate, accounts for at least 50% of the plasma and 60-70% of urinary excreted radioactivity.

Distribution

Plasma protein binding of pizotifen is over 90%. The distribution volume in man is 833L and 70L for pizotifen and N-glucuronide conjugate, respectively.

Elimination

Excretion of pizotifen by the feces is equivalent to about one-third of the given oral dose. Less than 1% of the administered dose is excreted unchanged in the urine, whereas up to 55% is excreted as metabolites. The elimination half-life for pizotifen and N-glucuronide conjugate is about 23 hours.

TOXICOLOGY

Acute Toxicity:

Acute toxicity studies were conducted in mice, rats and rabbits:

LD₅₀ (mg/kg)

Mouse		Rat		Rabbit	
Oral	I.V.	Oral	I.V.	Oral	I.V.
880	43	1500	17	700	19
±102	±2	±330	±1	±252	±2

Signs of toxicity after oral administration to mice and rats included motor disturbances (ataxia, jumping, twitching, sporadic convulsions, hyperreflexia), ventral decubitus, prostration, stupor, dyspnea and bradypnea. The signs lasted several hours in mice and up to 60 hours in rats. In rabbits, ventral decubitus, weakness and drooping of the head were observed. In all three species prior to death, ataxia, ventral or lateral decubitus, convulsions, dyspnea, paralysis and cyanosis were observed.

Chronic Toxicity:

Chronic oral toxicity studies were done in both rats and dogs for durations of 26 weeks and two years.

Pizotifen was administered orally to rats at 3 dosage levels (5, 16 and 55 mg/kg/day) for 26 weeks. Weights of livers, adrenals and thyroids were increased in the high-dose group and there were mild signs of dose-dependent, centrolobular hepatic lipidosis and thyroidal hyperactivity in the mid and high-dose groups. There was no evidence of cholestasis.

Doses of 3, 9 and 27 mg/kg/day were administered to rats for 2 years. Cellular and clinical hematologic, ophthalmoscopic and histologic examinations did not indicate drug-induced abnormalities in animals sacrificed after 16 months. The only changes observed after 2 years of treatment were increased liver and kidney weights in high-dose females and increased liver weights in mid-dose females.

Pizotifen was administered to dogs at levels of 3, 10 and 30 mg/kg/day for 26 weeks. Increased relative organ weights of spleens, livers and thyroids were observed in the mid- and high-dose dogs. Microscopy indicated thyroidal hyperactivity and increased hepatic cellular turnover in a high-dose dog. Serum alkaline phosphatase was slightly increased in one mid-dose and one high-dose dog at the end of the experiment. There was no evidence of cholestasis.

Doses of 1, 3 and 9 mg/kg/day also were administered to dogs for 2 years. Mean SGPT values were increased in high-dose dogs compared to control means. Other liver function tests were within normal range. The effect was more pronounced in males. Concomitant histopathologic changes were not evident.

Reproductive Studies:

Pizotifen was administered orally at the dose levels of 3, 10, and 30 mg/kg/day to female rats and rabbits from the 6th to 15th, and 6th to 18th days of pregnancy respectively. The animals were sacrificed at term and examined together with their fetuses. Embryotoxic or teratogenic drug effects could not be detected in either animal species. Male and female fertility tests were done. Conception rates, litter sizes and litter weights were not affected.

BIBLIOGRAPHY

CLINICAL

1. Arthur, G.P.: "The Treatment of Migraine with BC-105 (Sandomigran). A double-blind trial", *New Zealand Medical Journal*, 73:5-9, 1971.
2. Briars G.L., Travis S.E., Anand B., Kelly A.M.: "Weight gain with pizotifen therapy". *Arch. Dis. Child.* 93:590-593, 2008.
3. Carroll JD, Maclay WP.: "Pizotifen (BC 105) in migraine prophylaxis." *Current Medical Research and Opinion*, 3(2):68-71, 1975.
4. Cerbo R., Casacchia M., Formisano R., Feliciani M., Cusimano G., Buzzi M.G., Agnoli A.: "Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis." *Cephalgia* 6:15-18, 1986.
5. Doughty M.J., Lyle W.M.: "Medications used to prevent migraine headaches and their potential ocular adverse effects" *Optometry and Vision Science*, 72:879-91, 1995.
6. Elouni B, Ben Salem C, Zamy M, Poupon R, Bouraoui K, Biour M. Fulminant hepatitis possibly related to pizotifen therapy. *Ann Pharmacother.*; 44(7-8):1348-9, 2010.
7. Griffiths N.D., Penn N.D., Tindall H.: "A report of acute Overdosage of the anti-serotonergic drug pizotifen." *Postgraduate Medical Journal*; 63:59-60, 1987
8. Godin, O.: "Notes sur l'essai clinique du BC-105 Sandoz dans la migraine et la céphalée de Horton". *Ars Medici. Nouveautés médicales, pour le médecin praticien.* 24:991-1003, 1969.
9. Hornabrook, R.W., et al.: "Trial of a Serotonin Inhibitor BC-105 in the Prevention of Migraine". *New Zealand Medical Journal*, 70:387-390, 1969.
10. Hughes, R.C.: "BC-105 in the Prophylaxis of Migraine". *Current Therapeutic Research*, 13:63-68, 1971.
11. Jowett N.: "Severe weight loss after withdrawal of chronic pizotifen treatment." *J Neurol Neurosurg Psychiatry.* 65(1):137, 1998;
12. Lance, J.W., et al.: "Clinical trial of a new serotonin antagonist, BC-105, in the prevention of migraine". *Med. J. Aust.* 1:54-55, 1968.
13. Ryan, R.E.: "BC-105 A New Preparation for the Interval Treatment of Migraine - A Double-blind Evaluation Compared with a Placebo". *Headache*, 11:6-18, 1971.
14. Ryan, R.E.: "Double-blind Crossover Comparison of BC-105, Methysergide and Placebo in the Prophylaxis of Migraine Headache". *Headache*, 8:118-126, 1968.
15. Schaer, J.: "BC-105 - A New Serotonin Antagonist in Treatment of Migraine". 10:67-73, 1970.
16. Selby, G.: "A Clinical Trial of An Antiserotonin Drug, BC-105, in the Prophylaxis of Migraine". *Proc. Aust. Assoc. Neurologists*, 7:37-44, 1970.
17. Sicuteri, F., et al.: "An Antaminic Drug, BC-105, in the Prophylaxis of Migraine". *Int. Arch. Allergy*, 31:78-93, 1967.
18. Sjaastad, O., et al.: "Appraisal of BC-105 in migraine prophylaxis". *Acta Neurol. Scandinav.*, 45:594-600, 1969.

19. Vilming S, Standnes B, Hedman C.: "Metoprolol and pizotifen in the prophylactic treatment of classical and common migraine. A double-blind investigation." *Cephalalgia*; 5:17-23, 1985.

PRECLINICAL

1. Bagdon, R.E., et al.: "The Influence of Maturation on the Acute Toxicity to Rats of the Serotonin Antagonists Sandomigran (BC-105) and Cyproheptadine". *Pharmacologist* 12:297, 1970.
2. Gauthier, J.C., et al.: "Thromboses plaquettaires expérimentales dans les artères cérébrales. Effets du dipyridamole, de dérivés de l'ergot de seigle et d'antisérotinines". *Presse méd.* 78:1775-1780, 1970.

PART III: CONSUMER INFORMATION**^{Pr}Sandomigran & ^{Pr}Sandomigran DS
Pizotifen Tablets (as hydrogen malate)**

This leaflet is part III of a three-part "Product Monograph" published when Sandomigran & Sandomigran DS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandomigran or Sandomigran DS. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Sandomigran is prescribed for the prevention of migraine.

What it does:

When Sandomigran is taken regularly it can help to reduce the frequency or severity of migraine. Sandomigran is not intended for the treatment of acute migraines or to stop migraine attacks once they have started.

When it should not be used:

Do not use Sandomigran if you:

- are allergic to this medicine, or to any of the components of its formulation (for a list of components, see the section "What the nonmedicinal ingredients are");
- take a monoamine oxidase inhibitor for treatment of depression (e.g.: Nardil[®], Parnate[®], Zynoxam[®]);
- have a problem with food passing out of the stomach either from a complete or partial obstruction (pyloro-duodenal obstruction);
- have an ulcer;
- have intolerance to the sugar of milk products (or lactose).
- are less than 12 years old

What the medicinal ingredient is:

Pizotifen hydrogen malate

What the nonmedicinal ingredients are:

Each 0.5 mg tablet contains: lactose monohydrate, corn starch, povidone, magnesium stearate, propyl paraben, acacia, colloidal silicone dioxide, cetyl palmitate, sugar and talc.

Each 1 mg tablet contains: lactose anhydrous, magnesium stearate, and microcrystalline cellulose.

What dosage forms it comes in:

Tablets; 0.5 mg (Sandomigran), 1 mg (Sandomigran DS)

WARNINGS AND PRECAUTIONS

Keep Sandomigran out of the reach of children. You should not give Sandomigran to anyone as inappropriate use may have severe medical consequences.

BEFORE you use Sandomigran talk to your doctor or pharmacist if you:

- You have raised pressure in your eyes (glaucoma);
- You have difficulty urinating;
- You have a kidney or liver disease;
- You have diabetes or heart disease
- You have a history of seizure/epilepsy (convulsions)
- You are pregnant, planning to become pregnant or you become pregnant while taking this medication.
- You are breastfeeding or plan to breastfeed.
- You have intolerance of sugar or lactose

Driving and operating machinery

Sandomigran may impair the mental and/or physical abilities required for performance of potentially hazardous task such as driving a car or operating machinery. If you experience drowsiness or dizziness, such tasks should be avoided.

Avoid alcoholic beverages or taking medications that can cause drowsiness (including sleeping pills, cold syrup, antidepressants etc.) while taking Sandomigran as they can increase the effect of drowsiness and dizziness.

Take this medication as directed by your doctor. Do not stop Sandomigran or Sandomigran DS without advice by your physician. Sudden stoppage of this drug may cause acute withdrawal reactions. Symptoms may include depression, tremor, nausea, anxiety, and/or sleep disorder etc.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other prescription or over-the-counter medicines, vitamins or natural health products during your treatment with Sandomigran.

Drugs that may interact with Sandomigran & Sandomigran DS include:

- Alcohol;
- Sleeping pills, sedatives and antihistamines drugs (e.g. cold and hay fever medicines)
- Low blood pressure drugs
- Monoamine oxidase inhibitor (MAOI)

PROPER USE OF THIS MEDICATION

Adult and elderly:

The starting dose of Sandomigran is 0.5 mg once daily at bedtime. The daily dose can be increased gradually to a total dose of 1.5 mg administered at bedtime or in three divided doses if recommended by your physician. Up to 3 mg may be given as a single dose.

Children (12 years and older):

The starting dose of Sandomigran is 0.5 mg once daily at bedtime. A maximum single dose of 1 mg can be given at bedtime. The overall daily dose can be increased gradually up to 1.5 mg divided into three 0.5 mg doses if recommended by your physician.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The symptoms of overdose may include sedation, drowsiness rapid heart rate, nausea, vomiting and lack of coordination of muscle movement.

Missed Dose:

If you normally take Sandomigran tablets 2 or more times a day you should take the last dose you missed as soon as you remember. Do not take it if there is less than 4 hours before your next dose, but go back to your regular dosing schedule. Do not double doses or take more than your maximum daily dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of Sandomigran are: increased appetite, weight gain, drowsiness, nausea, dry mouth, fatigue and dizziness.

Other side effects such as the following have also been observed: constipation, skin irritation, insomnia, anxiety, muscle and joint pain, muscle cramps, delayed menstrual period, breast changes (pain, enlargement, secretion).

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

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and seek emergency medical help
		Only if severe	In all cases	
Rare or very rare	Yellowing of the skin or eyes (jaundice)		√	
	Persistent sad mood	√		
	Aggressive behaviour or agitation in children	√		
	Convulsions (seizures) or hallucination			√
	Sensation of tingling and/or pricking		√	
	Partial or complete loss of vision		√	
Unknown	Allergic reaction (symptoms include swelling in the mouth, tongue, face, and throat, itching, rash, blistering of the skin, and/or mucous membranes of the lips, eyes, mouth nasal passages or genitals)			√

This is not a complete list of side effects. For any unexpected effects while taking Sandomigran or Sandomigran DS, contact your physician or pharmacist.

HOW TO STORE IT

- store your Sandomigran tablets at room temperature (between 15-30°C)
- protect from exposure to light and moisture
- keep out of reach and sight of children
- discard any expired medicine or medicine no longer needed

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

-
- Report online at www.healthcanada.gc.ca/medeffect
 - Call toll-free at 1-866-234-2345
 - Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.website.document>

or by contacting the sponsor, Paladin Labs Inc., at:
1-800-550-6060

This leaflet was prepared by Paladin Labs Inc.

Last revised: October 30, 2012