PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]SANDOMIGRAN DS

Pizotifen tablets

Tablets, 1 mg pizotifen (as pizotifen malate), oral

Serotonin and Tryptamine Antagonist

Migraine Prophylaxis

ATC code: N02CX

Paladin Labs Inc.
100 Alexis Nihon Blvd., Suite 600
Saint-Laurent, Quebec, Canada
H4M 2P2

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	08/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SANDOMIGRAN DS (pizotifen tablets) is indicated 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 DS and in most trials it was more effective than placebo in reducing the frequency or severity of attacks.

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

1.1 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SANDOMIGRAN DS in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS).

Adolescents (12-17 years of age): There is limited evidence supporting the safety and efficacy of SANDOMIGRAN DS in adolescents 12-17 years of age, therefore SANDOMIGRAN DS should be used with caution in this age group (see 4.2 Recommended Dose and Dosage Adjustment).

1.2 Geriatrics

Geriatrics (>65 years of age): The safety and efficacy of SANDOMIGRAN DS in patients 65 years of age or older have not been established. Caution should be exercised with the use of SANDOMIGRAN DS 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.

2 CONTRAINDICATIONS

SANDOMIGRAN DS (pizotifen tablets) is contraindicated in:

- patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of such therapy as it may prolong and intensify the anticholinergic effects of antihistaminic substances (see 9.4 Drug-Drug Interactions).
- patients with pyloroduodenal obstruction and stenosing pyloric ulcer.
- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- children under the age of 12.

4 DOSAGE AND ADMINISTRATION

4.1 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 DS 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 DS decrease after a period of time in a certain number of patients.

- SANDOMIGRAN DS coated tablets contain lactose. Its use is not recommended in patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

4.2 Recommended Dose and Dosage Adjustment

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 3 mg may be given as a single dose. The average maintenance dose is 1.5 mg/day.

Pediatrics (<12 years of age): SANDOMIGRAN DS is contraindicated in children under the age of 12.

Adolescents (12-17 years of age): SANDOMIGRAN DS may be prescribed to 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 1 mg can be given at night. Daily doses up to a maximum of 1.5 mg may be given in divided doses.

4.5 Missed Dose

If a dose is missed and the patient normally takes SANDOMIGRAN DS tablets 2 or more times a day, the patient should be instructed to take the last dose they missed as soon as they remember. However, if there is less than 4 hours left before the next scheduled dose, the patient should go back to their regular dosing schedule and skip the missed dose. The patient should not double doses or take more than the maximum daily dose.

5 OVERDOSAGE

Adults: The symptoms of overdosage 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. 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 DS 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 1 mg pizotifen (as pizotifen malate)	Lactose anhydrous, magnesium stearate, and microcrystalline cellulose

1 mg tablets: Each whitish with bevelled edge, scored on one side and embossed with the Paladin shield logo on the other side of the tablet.

SANDOMIGRAN DS is supplied in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Patients with cardiovascular disease should be given SANDOMIGRAN DS with caution, and appropriate laboratory tests should be done at regular intervals.

Dependence/Tolerance

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

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 8 ADVERSE REACTIONS).

Driving and Operating Machinery

Patients should be warned that SANDOMIGRAN DS 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 DS 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.

Endocrine and Metabolism

Patients with diabetes should be given SANDOMIGRAN DS with caution, and appropriate laboratory tests should be done at regular intervals.

SANDOMIGRAN DS coated tablets contain lactose. Its use is not recommended in patients with rare hereditary problems of galactose intolerance, lactase deficiency, or glucose-galactose malabsorption.

Effects on Weight: SANDOMIGRAN DS 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.

Hepatic/Biliary/Pancreatic

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. SANDOMIGRAN DS should be discontinued if there is any clinical evidence of hepatic dysfunction during treatment and until the cause of the liver abnormality is determined.

Neurologic

Drowsiness (including somnolence and fatigue) is among the most common side effects with SANDOMIGRAN DS use. A gradual increase in the dosage of SANDOMIGRAN DS is recommended to minimize or reduce the incidence of drowsiness.

Anticholinergic effects: In view of the weak anticholinergic effect of SANDOMIGRAN DS, caution is required in patients with narrow-angle glaucoma (see 7 WARNINGS &PRECAUTIONS, Ophthalmologic) or with a predisposition to urinary retention (e.g., prostatic hypertrophy).

Epilepsy: Seizures as undesirable effects have been observed more frequently in patients with epilepsy. SANDOMIGRAN DS should be used with caution in patients with epilepsy.

Ophthalmologic

A limited number of cases of lens opacities have been reported but did not appear to be drug-related. SANDOMIGRAN DS 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 health professional for further investigation.

Caution is required in patients with narrow-angle glaucoma (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Anticholinergic effects). 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.

Renal

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

Caution is required in patients with a predisposition to urinary retention (e.g., prostatic hypertrophy) (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Anticholinergic effects).

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (<12 years of age): SANDOMIGRAN DS is contraindicated in children under the age of 12 (see 2 CONTRAINDICATIONS).

Adolescents (12-17 years of age): There is limited evidence supporting the safety and efficacy of SANDOMIGRAN DS in adolescents 12-17 years of age, therefore SANDOMIGRAN DS should be used with caution in this age group (4.2 Recommended Dose and Dosage Adjustment, Adolescents).

7.1.4 Geriatrics

The safety and efficacy of SANDOMIGRAN DS in patients 65 years of age or older have not been established. Caution should be exercised with the use of SANDOMIGRAN DS 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Increased appetite, weight gain and drowsiness (including somnolence and fatigue) are the most common side effects. Health professionals should be aware of the potential negative effects of SANDOMIGRAN DS in special populations already with an excess in weight or in normal weight population where an excess in weight could be deleterious (e.g., arterial hypertension, diabetes mellitus, and hypercholesterolemia). A gradual increase in the dosage of SANDOMIGRAN DS is recommended to minimize or reduce the incidence of drowsiness (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

8.5 Post-Market Adverse Reactions

Table 2 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 2 – 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 DS 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 DS:

Hepatobiliary disorders: Fulminant hepatitis, hepatitis, jaundice.

Investigations: Hepatic enzyme increased.

Musculoskeletal and connective tissue disorders: Muscle cramps.

Nervous system disorders: Sedation.

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
Do not use SANDOMIGRAN DS in patients currently using a monoamine oxidase inhibitor (MAOI) or within 14 days of such therapy (see 2 CONTRAINDICATIONS; 9.4 Drug-Drug Interactions).

9.2 Drug Interactions Overview

SANDOMIGRAN DS should not be consumed with alcohol, as it may enhance the central effects of alcohol, such as drowsiness and dizziness (see 9.3 Drug-Behavioral Interactions).

SANDOMIGRAN DS may interact with central nervous systems agents, antihypertensives and monoamine oxidase inhibitors (see 9.4 Drug-Drug Interactions). In addition, given that pizotifen is extensively metabolized by the liver, primarily by N-glucuronidation, increased plasma concentration of pizotifen upon concomitant administration of drugs which exclusively undergo glucuronidation cannot be excluded.

9.3 Drug-Behavioral Interactions

The concomitant use of alcohol should be avoided. SANDOMIGRAN DS may increase central effects of alcohol, such as drowsiness and dizziness.

9.4 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Central Nervous System (CNS) agents	T	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	T	SANDOMIGRAN DS may reduce the efficacy of	Patient blood pressure monitoring is

		antihypertensive medications (adrenergic neurone blockers) as it antagonizes their hypotensive effect.	recommended.
Monoamine Oxidase Inhibitors (MAOIs) (e.g., linezolid, methylene blue, moclobemide, phenelzine, procarbazine, and tranylcypromine)	T	MAOIs can prolong and intensify the anticholinergic effects of antihistaminic substances.	Concomitant use with MAOIs or use within 14 days of such therapy should be avoided (see 2 CONTRAINDICATIONS).

Legend: T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Pizotifen 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 pizotifen malate 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. Pizotifen malate also inhibits serotonin re-uptake by blood platelets, impacting tonicity and decreasing passive distension of extracranial arteries.

10.2 Pharmacodynamics

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.

10.3 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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

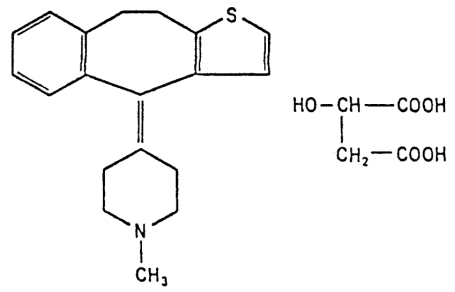
Drug Substance

Proper name: Pizotifen malate

Chemical name: 4 -(9,10-Dihydro-4H-benzo[4,5] cycloheptal [1,2-b]thien-4-ylidene)-1-methylpiperidine malate

Molecular formula and molecular mass: $C_{19}H_{21}NS.C_4H_6O_5$; 429.5

Structural formula:



Physicochemical properties: Pizotifen malate is a white to yellowish crystalline powder, readily soluble in water and organic solvents.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity:

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

LD_{50} (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 and Developmental Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]SANDOMIGRAN DS

pizotifen tablets

Read this carefully before you start taking **SANDOMIGRAN DS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SANDOMIGRAN DS**.

What is SANDOMIGRAN DS used for?

SANDOMIGRAN DS is used in adolescents (12 to 17 years of age) and adults to prevent migraines.

How does SANDOMIGRAN DS work?

Migraine headaches are believed to be caused by a widening of the blood vessels in the head. SANDOMIGRAN DS is thought to affect certain chemicals in the brain, which in turn prevent blood vessels from widening and may also change our sensitivity to pain. This helps to prevent and reduce the number of migraines. SANDOMIGRAN DS does not treat migraines or stop them once they have started.

What are the ingredients in SANDOMIGRAN DS?

Medicinal ingredient: Pizotifen malate
Non-medicinal ingredients: Lactose anhydrous, magnesium stearate and microcrystalline cellulose

SANDOMIGRAN DS comes in the following dosage forms:

Tablets: 1 mg

Do not use SANDOMIGRAN DS if:

- you are allergic to pizotifen or to any of the other ingredients in SANDOMIGRAN DS.
- you are currently taking or have taken in the last 14 days a monoamine oxidase inhibitor (MAOI) medication (such as linezolid, methylene blue, moclobemide, phenelzine, procarbazine, and tranylcypromine).
- you have a problem with food passing from the stomach into the small intestine either from a complete or partial blockage (pyloro-duonenal obstruction). This includes ulcers that narrow the opening from the stomach into the small intestines (stenosing pyloric ulcer).
- you are less than 12 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SANDOMIGRAN DS. Talk about any health conditions or problems you may have, including if you:

- have glaucoma (an eye condition usually caused by high pressure in the eye).
- have difficulty urinating.
- have kidney or liver problems.
- have diabetes or heart problems.
- have epilepsy or seizures (sudden and uncontrolled burst of electrical activity in the brain)
- are at risk of excessive weight changes.
- are pregnant, think you might be pregnant, or planning to become pregnant.
- are breastfeeding or plan to breastfeed.
- have one of the following rare genetic conditions:
  - Galactose intolerance
  - Lactase deficiency
  - Glucose-galactose malabsorption

  SANDOMIGRAN DS contains lactose.

Other warnings you should know about:

Stopping your treatment: Do not suddenly stop taking SANDOMIGRAN DS without first talking to your healthcare professional. If you do this, it may cause withdrawal symptoms such as depression, shaking (tremor), nausea, anxiety, a general feeling of discomfort, dizziness, sleep problems, fainting, loss of appetite and rapid weight loss. Stopping your treatment should be a gradual process that you discuss with your healthcare professional.

Tolerance: You may develop a tolerance to SANDOMIGRAN DS if you have taken it for a long time. Tell your healthcare professional if you feel like SANDOMIGRAN DS no longer works as well as it once did. They may increase your dose.

Weight: You may experience weight gain while taking SANDOMIGRAN DS. Monitor your weight on a regular basis during your treatment. You may experience weight loss after stopping your treatment.

Driving and using machinery: SANDOMIGRAN DS may cause dizziness, sleepiness, or a lack of energy. Do not drive, use machinery, or do activities that require you to be alert until you know how SANDOMIGRAN DS affects you.

Pregnancy: It is not known if SANDOMIGRAN DS can harm your unborn baby. Only take SANDOMIGRAN DS during pregnancy if you and your healthcare professional have discussed the risks and have decided that you should. If you discover that you are pregnant while taking SANDOMIGRAN DS, tell your healthcare professional **right away**.

Breastfeeding: SANDOMIGRAN DS can pass into breast milk and may harm a breastfed baby. Therefore, SANDOMIGRAN DS is not recommended during breastfeeding. Talk to your healthcare professional about the best way to feed your baby during this time.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take SANDOMIGRAN DS if you: • are taking or have recently taken (in the last 14 days) any MAOIs such as linezolid, methylene blue, moclobemide, phenelzine, procarbazine, and tranylcypromine. Ask your healthcare professional if you are unsure.

The following may also interact with SANDOMIGRAN DS:

- central nervous system (CNS) depressant used to slow down the nervous system. These can include:
  - medicines used to help reduce anxiety.
  - medicines used to treat depression, psychotic symptoms, or other mental health disorders.
  - sleeping pills.
  - medicines used to treat allergies.
  - cough and cold medicines.
- medicines used to lower blood pressure.
- alcohol. SANDOMIGRAN DS may lower your alcohol tolerance. This means you may feel the effects of alcohol when taking less alcohol than usual. Drinking alcohol while taking SANDOMIGRAN DS may increase your risk of dizziness and sleepiness. It is best not to drink alcohol at all while taking SANDOMIGRAN DS to avoid side effects.

How to take SANDOMIGRAN DS:

- Take SANDOMIGRAN DS exactly as prescribed by your healthcare professional.
- The effects of your medicine may not be noticeable in the first few weeks of treatment. If you are concerned that your medicine is not working:
  - continue taking your medicine as prescribed as it may take some time for SANDOMIGRAN DS to work; and
  - discuss this with your healthcare professional.
- Do not stop taking SANDOMIGRAN DS without talking to your healthcare professional first. Stopping SANDOMIGRAN DS suddenly may cause unwanted side effects.

Usual dose:

Adults:

- The starting dose is 0.5 mg once daily at bedtime.
- Your daily dose may be gradually increased to the usual maintenance dose of 1.5 mg at bedtime or in three divided doses.

- The dosage range is 1 mg to 6 mg daily. Up to 3 mg may be given in a single dose.

Adolescents (12 to 17 years of age):

- The starting dose is 0.5 mg once daily at bedtime.
- A maximum single dose of 1 mg can be given at bedtime.
- The total daily dose may be gradually increased up to 1.5 mg given in divided doses.

Overdose:

Symptoms of an overdose with SANDOMIGRAN DS may include:

- dry mouth
- dilated pupils
- drowsiness
- dizziness
- low blood pressure
- nausea or vomiting
- fast heartbeat
- difficulty breathing
- lack of coordination
- confusion
- feeling agitated or restless
- seizures
- coma

If you think you, or a person you are caring for, have taken too much SANDOMIGRAN DS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you normally take SANDOMIGRAN DS tablets 2 or more times a day, you should take the last dose you missed as soon as you remember. However, if there is less than 4 hours left before your next dose, skip the missed dose and take your next dose at the usual time. Do not double doses or take more than your maximum daily dose.

What are possible side effects from using SANDOMIGRAN DS?

These are not all the possible side effects you may have when taking SANDOMIGRAN DS. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- increased appetite, which may lead to weight gain
- drowsiness
- lack of energy
- dizziness
- nausea or vomiting
- dry mouth
- constipation
- muscle or joint pain

- sleep problems
- feeling anxious
- absence of menstrual periods in females
- breast pain or growth, production of breast milk

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Liver disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite		✓	
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide	✓		
Aggressive behaviour or agitation in adolescents	✓		
Hallucinations: seeing or hearing things that are not there			✓
Sensation of tingling and/or pricking		✓	
Eye problems: increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, changes in vision (hazy, blurred or double vision, sudden sight loss), dilated pupils		✓	
VERY RARE			
Seizures (fits): loss of consciousness with uncontrollable shaking			✓
UNKNOWN FREQUENCY			
Allergic reaction: swelling in the mouth, tongue, face, and throat, itching, rash, blistering of the skin,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
and/or mucous membranes of the lips, eyes, mouth nasal passages or genitals			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

- Store your SANDOMIGRAN DS tablets at room temperature (between 15°C - 30°C).
- Protect from light and moisture.
- Keep out of reach and sight of children.

If you want more information about SANDOMIGRAN DS:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.paladinlabs.com, or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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