NOVARTIS

Drug Regulatory Affairs

SANDOMIGRAN® (pizotifen)

0.5 mg and 1.5 mg coated tablets

MOSEGOR® (pizotifen)

0.5 mg coated tablets and 0.5 mg/10 mL syrup

Summary of Product Characteristics (SmPC)

Version 2.0

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1 Trade name

SANDOMIGRAN® 0.5 mg and 1.5 mg coated tablets.

MOSEGOR® 0.5 mg coated tablets; 0.5 mg/10 ml syrup.

2 Description and composition

Pharmaceutical forms

SANDOMIGRAN

Tablets for oral administration.

MOSEGOR

Tablets for oral administration.

Syrup for oral administration.

Information might differ in some countries.

SANDOMIGRAN, MOSEGOR

Active substance

The active ingredient is 4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo-[4,5]cyclohepta[1,2-b] thiophene hydrogen malate (= pizotifen hydrogen malate).

SANDOMIGRAN

One coated tablet contains 0.73 mg pizotifen hydrogen malate (corresponding to 0.50 mg pizotifen base) or 2.19 mg pizotifen hydrogen malate (corresponding to 1.5 mg pizotifen base).

MOSEGOR

One coated tablet contains 0.73 mg pizotifen hydrogen malate (corresponding to 0.50 mg pizotifen base).

10 mL syrup contain 0.73 mg pizotifen hydrogen malate (corresponding to 0.50 mg pizotifen base).

Active moiety

Pizotifen

Excipients

SANDOMIGRAN

Sandomigran 0.5 mg coated tablets:

Tablet core: magnesium stearate; talc; povidone; maize starch; lactose, monohydrate.

Coating: titanium dioxide (E171); silica, colloidal anhydrous; acacia; talc, sucrose, cetyl palmitate.

Sandomigran 1.5 mg coated tablets:

Tablet core: magnesium stearate; talc; povidone; maize starch; lactose, monohydrate.

Coating: iron oxide yellow (E172); iron oxide black (E172); shellac; titanium dioxide (E171); carnauba wax; silica, colloidal anhydrous; acacia; talc; sucrose.

MOSEGOR

Mosegor 0.5 mg coated tablets:

Tablet core: magnesium stearate; talc; povidone; maize starch; lactose, monohydrate.

Coating: titanium dioxide (E171); silica, colloidal anhydrous; acacia; talc, sucrose, cetyl palmitate.

Mosegor 0.5 mg/10 mL syrup: propyl parahydroxybenzoate (E216); methyl parahydroxybenzoate (E218); citric acid, anhydrous; disodium hydrogen phosphate, anhydrous; ethanol 96%; sucrose; sorbitol 70%; water, purified; mandarine and lemon flavoring agents.

Information might differ in some countries.

3 Indications

SANDOMIGRAN

Prophylactic treatment of recurrent vascular headaches, such as

- typical or atypical migraine
- cluster headache.

The International Classification of Headache Disorders 2nd edition (ICHD-II) are standard classifications of headache used by health professionals and describe the above-mentioned disorders as follows: prophylactic treatment of recurrent migraine headache with or without aura and of cluster headache.

Sandomigran is not effective in relieving migraine attacks once in progress.

MOSEGOR

- Anorexia of somatic or psychogenic origin in underweight patients, supplementary to the treatment of the underlying condition, such as infectious or parasitic diseases (including convalescence), chronic diarrhea, anorexia nervosa or depressive states in the elderly.
  Note: Priority should always be given to identifying and treating the underlying cause.

4 Dosage and administration

Dosage

General target population

SANDOMIGRAN

Starting with 0.5 mg per day, the dosage should be progressively increased. The average maintenance dosage is 1.5 mg daily in divided doses or as a single dose at night. In refractory cases the physician may gradually raise the dosage to 3 to 4.5 mg daily taken in 3 divided doses.

MOSEGOR

Underweight patients with anorexia

Starting with 0.5 mg per day, the dosage should be progressively increased up to 0.5 mg three times daily.

Pediatric patients (aged 2 years and above)

SANDOMIGRAN

Starting with 0.5 mg, the daily dose may be increased up to 1.5 mg in divided doses, or 1 mg may be given as a single dose at night.

Children below two years of age should not be given Sandomigran

MOSEGOR

Small initial doses should be gradually increased up to an average total daily maintenance dosage of 0.025 mg per kg body weight; this dose may be given in 2 or 3 divided doses or as directed by the physician.

Approximate daily dose:

- Age 2 to 6 years: 5 to 10 mL syrup (0.25 to 0.50 mg)

  Examples of the total daily dose, in milliliters of the syrup, for children having body weights often seen in the 2-6 year old group include: 2 years old or 14 kg = 7 mL; 3 years old or 16 kg = 8 mL; 4 years old or 18 kg = 9 mL; 5 years old or 20 kg = 10 mL; 6 years old but less than 23 kg = 10 mL.
- Age 6 to 12 years: 10 to 20 mL syrup (0.50 to 1.0 mg)

  Examples of the total daily dose, in milliliters of the syrup, for children having body weights often seen in those aged 6 years and older include: 6 years old or 23 kg or more = 11 mL; 7 years old or 26 kg = 13 mL; 8 years old or 30 kg = 15 mL; 9 years old or 35 kg = 17 mL; 10 to 12 years old or around 40 kg = 20 mL.
- Children who are above 13 years of age or older with a body weight greater than 40 kg and can swallow tablets can be given the adult dose of Mosegor tablets in divided doses starting with one tablet of 0.5 mg daily and progressively increased as needed up to 0.5 mg three times daily.

Children below two years of age should not be given Mosegor.

Special populations

SANDOMIGRAN, MOSEGOR

Geriatric patients (aged 65 years and above)

There is no evidence to suggest that the dosage needs to be adjusted in elderly patients.

Renal and hepatic impairment

Caution is required in patients with renal or hepatic impairment and dosage adjustment may be necessary (see section 11 Clinical pharmacology / Pharmacokinetics / Special population).

5 Contraindications

SANDOMIGRAN, MOSEGOR

Known hypersensitivity to pizotifen or to any of the excipients (see section 2 Description and Composition / Excipients).

Sandomigran, Mosegor should not be given to children under 2 years of age.

6 Warnings and precautions

SANDOMIGRAN, MOSEGOR

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**.**

In view of the slight anticholinergic effect of pizotifen, caution is required in patients with narrow-angle glaucoma (except those successfully treated by surgery) or urinary retention (e.g. in prostatic enlargement).

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

Withdrawal symptoms like depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decreased have been reported following abrupt cessation of pizotifen (see section 7 Adverse drug reactions), therefore gradual withdrawal is recommended.

MOSEGOR

Weight gain is dependent on adequate food intake, and anorexia must be differentiated from malnutrition.

Mosegor syrup contains 200 mg ethanol per 10 mL syrup. This should be taken into account for those suffering from alcoholism, in children, in pregnant or breast-feeding women and in high-risk groups such as patients with liver disease, or epilepsy.

Driving and using machines

SANDOMIGRAN, MOSEGOR

Pizotifen may cause sedation, somnolence, dizziness and other CNS effects. Therefore, caution should be exercised when driving or using machines.

Patients being treated with Sandomigran, Mosegor and presenting with sedation and/or somnolence episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk.

7 Adverse drug reactions

SANDOMIGRAN, MOSEGOR

The most common side effects are appetite stimulating effect, increase in body weight and sedation (including somnolence and fatigue).

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) including isolated reports.

Table 7-1 Adverse drug reactions

Immune system disorders	
Rare:	Hypersensitivity, face oedema
Metabolism and nutrition disorders	
Very common:	Increased appetite, weight increased
Psychiatric disorders	
Rare:	Depression, Central nervous system stimulation (e.g. aggression, agitation), hallucination, insomnia, anxiety
Nervous system disorders	
Common:	Sedation (including somnolence), dizziness
Rare:	Paraesthesia
Very rare:	Convulsion
Gastrointestinal disorders	
Common:	Nausea, dry mouth
Uncommon	Constipation
Skin and subcutaneous tissue disorders	
Rare:	Urticaria, rash
Musculoskeletal and connective tissue disorders	
Rare:	Myalgia
General disorders and administration site conditions	
Common	Fatigue

Adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified with pizotifen based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Hepatobiliary disorders

Unknown: Hepatic enzyme increased, jaundice, hepatitis

Musculoskeletal and connective tissue disorders

Unknown: Muscle cramps.

Withdrawal symptoms

Withdrawal reactions have been reported following abrupt cessation of pizotifen, therefore gradual withdrawal is recommended (see section 6 Warnings and precautions). Withdrawal symptoms may include: depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decreased.

8 Interactions

SANDOMIGRAN, MOSEGOR

The following drugs may exhibit drug interactions with pizotifen upon concomitant administration.

Anticipated drug interactions to be considered

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.

Cisapride

Concomitant administration of pizotifen with cisapride may lead to reduced efficacy of cisapride.

Central nervous system agents

Central effects of sedatives, hypnotics, antihistamines (including certain common cold preparations), and alcohol may be enhanced.

9 Women of child-bearing potential, pregnancy, breast-feeding and fertility

SANDOMIGRAN, MOSEGOR

Women of child-bearing potential

There is no data for recommendations in women of child-bearing potential.

Pregnancy

As clinical data for pizotifen in pregnancy are very limited, Sandomigran, Mosegor should be administered in pregnancy onlyif the expected benefits outweigh the potential risks.

Breast-feeding

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

Fertility

There were no fertility effects in a rat study with pizotifen hydrogen maleate (see section 13 Non-clinical safety data).

10 Overdosage

SANDOMIGRAN, MOSEGOR

Symptoms: drowsiness, nausea, dry mouth, tachycardia, pyrexia, hypotension, dizziness, excitatory states (in children), respiratory depression, convulsion (particularly in children), coma.

Treatment: Administration of activated charcoal is recommended; in case of very recent intake, gastric lavage may be considered. If necessary, symptomatic treatment should be given including monitoring of the cardiovascular and respiratory symptoms. For excitatory states or convulsions, benzodiazepines may be used.

11 Clinical pharmacology

ATC code

SANDOMIGRAN: Antimigraine drug, ATC code: N02C X01

MOSEGOR: Appetite stimulant drug, ATC code: A15.

Mechanism of action (MOA)

SANDOMIGRAN, MOSEGOR

Pizotifen is characterized by its polyvalent inhibitory effect on biogenic amines, such as serotonin, histamine and tryptamine.

Pharmacodynamics (PD)

SANDOMIGRAN

Pizotifen is suitable for the prophylactic treatment of migraine, reducing the frequency of attacks.

Pizotifen also possesses appetite-stimulating properties.

MOSEGOR

Pizotifen has an appetite-stimulating action suitable for increasing body weight in underweight anorectic patients. The compound is well tolerated, permitting treatment of anorexia both in children and adults.

Owing to its inhibitory effect on biogenic amines, pizotifen is also used for the prophylactic treatment of migraine.

Pharmacokinetics (PK)

SANDOMIGRAN, MOSEGOR

Absorption

Following oral administration, the drug is rapidly and almost completely absorbed from the gastrointestinal tract. The mean absolute bioavailability after oral administration is about 80%. Following a single 1-mg oral administration of pizotifen the mean maximum plasma concentration (Cmax) of pizotifen and its metabolite measured together were about 5 ng/mL (Tmax: 5.5 hr). Following repeated administration of 1mg three times a day for six days, the mean maximum plasma concentration at steady state was observed at 4 hr post dose (Cmax,ss: 14 ng/mL) and the mean trough plasma concentration was about 11 ng/mL (Cmin,ss).

Distribution

Pizotifen is extensively and rapidly distributed throughout the body with the mean distribution volume of 833 L and 70 L for the parent drug and its metabolite N-glucuronide, respectively. Approximately, 91% of the drug is bound to plasma proteins. The distribution and elimination kinetics have generally been described as a bi-exponential decay function using two-compartment model.

Metabolism

Pizotifen is extensively metabolized in the liver primarily by glucuronidation. The main metabolite is the N-glucuronide-conjugate and accounts for at least 50% of the plasma exposure.

Elimination

About one-third of an orally administered dose is excreted via the biliary route. A significant proportion of the parent drug, corresponding to about 18% of the administered dose, is found in the feces. The remaining fraction of the administered dose (about 55%) is primarily eliminated in the forms of metabolites in the urine. Less than 1% of the administered dose of pizotifen is excreted unchanged through the kidneys. Pizotifen and its major metabolite, N-glucuronide conjugate, is eliminated with a half-life of approximately 23 hours.

Special populations

Renal impairment

No specific pharmacokinetic studies were conducted in patients with renal impairment. Although pizotifen is primarily eliminated in the form of metabolites in the urine, the possibility of accumulation of inactive metabolites subsequently leading to the accumulation of the parent drug cannot be ruled out. Caution is required in patients with renal impairment and dosage adjustment may be necessary.

Hepatic impairment

Although no specific pharmacokinetic studies were conducted in patients with hepatic impairment, pizotifen is extensively metabolized in liver and primarily eliminated in the form of glucuronides in the urine. Caution is required in patients with hepatic impairment and dosage adjustment may be necessary.

12 Clinical studies

Sandomigran, Mosegor is an established product. The indications for treatment of anorexia and prophylactic use in migraine are supported by data from legacy clinical trials.

Weight gain was initially recorded as adverse effect during treatment of patients with recurring migraine headache. The weight gain properties of the drug in patients with anorexia of somatic or psychogenic origin have been documented primarily as secondary end point in legacy studies. The results from legacy studies (a total of 251 adults participated in seven randomized controlled studies and a total of 184 children participated in six randomised controlled studies) showed favorable effect on appetite stimulation and weight gain.

13 Non-clinical safety data

SANDOMIGRAN, MOSEGOR

Repeat-dose toxicity

Repeat-dose toxicity studies were performed in rats and dogs of up to 2 years duration. Target organs, based on histopathological findings, were liver, kidney and possibly thyroid in rats and liver, thyroid and spleen in dogs. The no-observed-effect level (NOEL) in both rats and dogs was 3 mg/kg which is over 30-fold greater than the maximum recommended human daily dose.

Reproductive toxicity

Pizotifen hydrogen malate was evaluated in multiple reproductive and developmental toxicity studies for its effects on fertility and its embryotoxic, fetotoxic, teratogenic and developmental toxic potential. There were no specific reproductive or developmental effects observed in mice, rats or rabbits up to the highest tested doses of 30 mg/kg. This dose level is greater than 300 times the daily maximum recommended adult human dose of 0.09 mg/kg. The study with

male and female rats did not identify any effects on fertility, litter size, survival rate or body weight gain of the offspring at the highest dose tested, 30 mg/kg.

Mutagenicity

In *vitro* and *in vivo* mutagenicity tests were performed and did not reveal any mutagenic activity of pizotifen hydrogen malate.

Carcinogenicity

A 2-year rat toxicity study did not reveal any gross lesions or masses attributable to pizotifen hydrogen malate administration at dose levels of up to 27 mg/kg which is 300 fold greater than the maximum recommended human daily dose on a mg/kg basis.

14 Pharmaceutical information

Incompatibilities

SANDOMIGRAN, MOSEGOR

Not applicable.

Special precautions for storage

SANDOMIGRAN, MOSEGOR

Sandomigran, Mosegor does not require any special storage conditions when stored in the original package.

Information might differ in some countries.

Sandomigran, Mosegor must be kept out of the reach and sight of children.

Instructions for use and handling

SANDOMIGRAN, MOSEGOR

Not applicable.

Special precautions for disposal

SANDOMIGRAN, MOSEGOR

Not applicable.

15 Supplier

Manufacturing site name and address: Novartis Farma S.p.A, Via Provinciale Schito 131, 80058 Torre Annunziata, Italy

Tel: +39 081 5354404

Email: giovanna.sepe@novartis.com