Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sanomigran 1.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg pizotifen as malate.

Excipients - contains Lactose Monohydrate 136.425mg and sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet
Ivory/yellow, sugar-coated, bi-convex tablets, printed ‘SMG 1.5’ on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylactic treatment of recurrent vascular headaches, including classical migraine, common migraine and cluster headache (periodic migrainous neuralgia).
Sanomigran is not effective in relieving migraine attacks once in progress.
The International Classification of Headache Disorders 2nd edition (ICHD-II) are standard classifications of headache used by healthcare professionals and describe the above-mentioned disorders as follows: prophylactic treatment of recurrent migraine headache with or without aura and of cluster headache.

4.2 Posology and method of administration

Oral administration.

Adults
Starting with 0.5mg daily, the dosage should be progressively increased. Dose is usually 1.5 mg daily. This may be taken as a single dose at night or in three divided doses, using 0.5 mg tablets or 1.5 mg tablets as appropriate. Dosage should be adjusted to individual patients' requirements up to a maximum of 4.5 mg daily. Up to 3 mg may be given as a single daily dose.

Children over 12 years:
Starting with 0.5mg daily, the dosage should be progressively increased. Dose is up to 1.5 mg daily, usually as a divided dose. Use of the 1.5 mg tablets is not recommended but up to 1 mg has been given as a single daily dose at night. 0.5 mg tablets may be used.

Use in the elderly
Clinical work with Sanomigran has not shown that elderly patients require different dosages from younger patients.

Special populations
Renal and hepatic impairment

Caution is required in patients with renal or hepatic impairment and dosage adjustment may be necessary (see section 5.2 Pharmacokinetic properties – Special population).

4.3 Contraindications

Hypersensitivity to pizotifen or to any of the excipients (see section 6.1 List of excipients).

Use in children under 12 years.

4.4 Special warnings and precautions for use

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 long half-life in the body and excretion in the urine, this drug should be used with caution in patients with renal dysfunction. The dosage interval may need to be prolonged.

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.

Sanomigran should be used with caution in patients with epilepsy and in patients receiving monoamine oxidase inhibitors.

Withdrawal symptoms like depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decreased have been reported following abrupt cessation of pizotifen (see section 4.8 Undesirable effects), therefore gradual withdrawal is recommended.

Sanomigran coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Sanomigran.

4.5 Interaction with other medicinal products and other forms of interaction

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 can not 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 by Sanomigran.
Sanomigran antagonises the hypotensive effect of adrenergic neurone blockers.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy should be avoided whilst taking this drug.

Lactation

Use in nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

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

Patients being treated with Sanomigran 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.

4.8 Undesirable effects

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, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), including isolated reports.

Table 1

Immune system disorders		
	Rare:	Hypersensitivity reactions, face oedema
Metabolism and nutrition disorders		
	Very common:	Increased appetite, weight increased
Psychiatric disorders		
	Rare:	Depression, CNS stimulation (e.g. aggression, agitation), hallucination, insomnia, anxiety
Nervous system disorders		
	Common:	Sedation (including somnolence), dizziness
	Rare:	Paraesthesia
	Very rare:	Seizures
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
Acute withdrawal reactions have been reported following abrupt cessation of Sanomigran therefore gradual withdrawal is recommended (see section 4.4 special warnings and precautions for use). Withdrawal symptoms may include: depression, anxiety, tremors, sleep disorder, nausea, malaise, dizziness and weight decreased.

4.9 Overdose

Symptoms:
Symptoms of overdosage may include drowsiness, dizziness, hypotension, dry mouth, confusion, excitatory states (in children), ataxia, nausea, vomiting, dyspnoea, cyanosis, tachycardia, pyrexia, convulsions (particularly in children), coma and respiratory paralysis.

Treatment:
Treatment should be directed to the elimination of the drug, administration of activated charcoal and diuresis is recommended. In case of very recent intake, gastric lavage may be considered. General surveillance measures are indicated, including monitoring of the cardiovascular and respiratory systems and symptomatic treatment may be required. Severe hypotension must be corrected (cave: adrenaline may produce paradoxical effects).

Excitatory states or convulsions may be treated with short-acting barbiturates or benzodiazepine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimigraine drug. ATC code: N02C X01.

Pizotifen is characterized by its polyvalent inhibitory effect on biogenic amines, such as serotonin, histamine and tryptamine. It is suitable for the prophylactic treatment of migraine, reducing the frequency of attacks.

Pharmacodynamic studies demonstrate pizotifen to have powerful anti-serotonin and antitryptaminic properties, marked antihistaminic effects and some antagonistic activity against kinins. It also possesses weak anticholinergic effects and sedative properties.

Pizotifen also possesses appetite-stimulating properties.

The prophylactic effect of Sanomigran in migraine is associated with its ability to modify the humoral mechanisms of headache. It inhibits the permeability-increasing effect of serotonin and histamine on the affected cranial vessels, thereby checking the transudation of plasmakinin so that the pain threshold of the receptors is maintained at 'normal' levels. In the sequence of events leading to the migraine attack, depletion of plasma serotonin contributes to loss of tone in the extracranial vessels. Pizotifen inhibits serotonin re-uptake by the platelets, thus maintaining plasma serotonin and preventing the loss of tone and passive distension of the extracranial arteries.

5.2 Pharmacokinetic properties

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 2-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). MetabolismPizotifen 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.

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.

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 faeces. 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 population
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 can not 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.

5.3 Preclinical safety data

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Maize starch
Povidone
Magnesium stearate
Talc

Coat
Sucrose
Acacia gum
Titanium dioxide (E171)
Colloidal anhydrous silica
Yellow iron oxide (E172)
Talc
Carnauba wax

Printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Keep the blister in the outer carton to protect from light.

6.5 Nature and contents of container

Opaque PVC/PVDC blister strips in cardboard outer carton containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs,
Suite 12, Bunkilla Plaza,
Bracetown Business Park,
Clonee,
Co. Meath.

8 MARKETING AUTHORISATION NUMBER

PA1113/012/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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