SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SANOMIGRAN Tablets 1.5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.175mg pizotifen hydrogen malate BP

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylactic treatment of recurrent vascular headaches, including classical migraine, common migraine and cluster headaches (periodic migrainous neuralgia).

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.

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

4.2 Posology and method of administration

Adults

Usually 1.5mg daily. This may be taken as a single dose at night or in three divided doses. Dosage should be adjusted to individual patient requirements up to a maximum of 4.5mg daily. Up to 3mg may be given as a single dose.

Children and adolescents from 2 years of age

Use of 1.5mg SANOMIGRAN Tablets is not recommended. The appropriate paediatric doses may be given using the 0.5mg SANOMIGRAN Tablets or SANOMIGRAN Elixir. For children SANOMIGRAN is available in an elixir form.

Use in the elderly
Clinical work with SANOMIGRAN has not shown elderly patients to 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).
Method of administration
Oral

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Although the anticholinergic activity of SANOMIGRAN is relatively weak, caution is required in the presence of closed angle glaucoma and in patients with a predisposition to urinary retention. Dosage adjustment may be necessary in patients with kidney insufficiency.

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.

Pizotifen should be used with caution in patients with a history of epilepsy.

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

Withdrawal symptoms like depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decrease have been reported following abrupt cessation of pizotifen, therefore gradual withdrawal is recommended.

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.

Central nervous system agents
The 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

Women of childbearing potential

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

Pregnancy

As clinical data with SANOMIGRAN in pregnancy are very limited it should only be administered during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding

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

Fertility

There were no fertility effects in a rat study with pizotifen hydrogen maleate.

4.7 Effects on ability to drive and use machines

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

Patients being treated with Sanomigran and presenting with drowsiness (including somnolence and fatigue) 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 drowsiness (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), unknown (frequency cannot be estimated from available data).

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
Hepatobiliary disorders		
	Unknown:	Hepatic enzyme increased, jaundice, hepatitis[*1]
Skin and subcutaneous tissue disorders		
	Rare:	Urticaria, rash
Musculoskeletal and connective tissue disorders		
	Rare:	Myalgia, arthralgia
	Unknown:	Muscle cramps[*1]
General disorders and administration site conditions		
	Common	Fatigue

[*1] These adverse events were reported in patients treated with pizotifen based on post-marketing spontaneous reports.

Withdrawal symptoms

Withdrawal reactions have been reported following abrupt cessation of pizotifen, therefore gradual withdrawal is recommended (see section 4.4 Special warnings and precautions for use). Withdrawal symptoms may include: depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decrease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any

suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Treatment: Administration of activated charcoal is recommended; in case of very recent uptake, gastric lavage may be considered. Severe hypotension must be corrected (CAVE: adrenaline may produce paradoxical effects). If necessary, symptomatic treatment should be given including monitoring of the cardiovascular and respiratory symptoms. Excitatory states or convulsions may be treated with short acting benzodiazepines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimigraine drug, ATC code: N02C X01

Pharmacodynamic studies demonstrate pizotifen to have powerful anti-serotonin and anti-tryptaminic properties, marked anti-histaminic effects and some antagonistic activity against kinins. It also possesses weak anti-cholinergic 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 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 bioavailablility after oral administration is about 78%. Following a single 1mg 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 metabolised 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 applied 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 the 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 (corresponding to 18 mg/m^2 in rats and to 60 mg/m^2 in dogs) which is, respectively, 5- and 18-times the maximum recommended human daily dose of 3.33 mg/m^2 based on body surface area comparisons.

Reproductive toxicity

Pizotifen hydrogen malate was evaluated in reproductive and developmental toxicity studies in mice, rats and rabbits. There were no effects on fertility or teratologic effects noted at all doses up to 30 mg/kg/day. At 10 and 30 mg/kg/day in mice there was a small decrease in fetal body weight in the presence of increased maternal mortality and in rats at the highest dose there was evidence of fetotoxicity.

Mutagenicity and Carcinogenicity

Pizotifen hydrogen malate was not genotoxic in standard in vitro and in vivo tests. Conventional rodent carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain lactose, maize starch, polyvinylpyrrolidone, magnesium stearate, talc (acid washed). The coating constituents are sugar (granulated no.2), talc, gum acacia, titanium dioxide, iron oxide yellow, carnauba wax, printing wax, colloidal anhydrous silica and purified water.

6.2 Incompatibilities

None

6.3 Shelf life

60 months

6.4 Special precautions for storage

Protect from direct light

6.5 Nature and contents of container

The tablets are ivory, circular, biconvex printed SMG 1.5 on one side and come in PVDC opaque blister packs containing 28 tablets.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

PHOENIX LABS
Suite 12, Bunkilla Plaza
Bracetown Business Park
Clonee, County Meath
IRELAND

8 MARKETING AUTHORISATION NUMBER(S)

PL 35104/0018

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28/04/1981 / 06/02/2009

10 DATE OF REVISION OF THE TEXT

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