SANDOMIGRAN®

1. NAME OF THE MEDICINE

SANDOMIGRAN® pizotifen 500 micrograms coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One coated tablet contains 725 micrograms pizotifen hydrogen malate (corresponding to 500 micrograms pizotifen base).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Biconvex sugar coated tablets and white colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SANDOMIGRAN® is indicated in adults and children from 2 years of age for the prophylactic treatment of recurrent vascular headaches, such as:

- typical or atypical migraine
- vasomotor headache
- cluster headache (Horton's syndrome)

Sandomigran is less effective in tension headache and in psychogenic and post-traumatic headaches. It is not effective in relieving migraine attacks once in progress.

4.2 Dose and method of administration

General target population
Starting with 0.5 mg daily, 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.

Special populations

Paediatrics (children from 2 years of age and adolescents)
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.

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 *Pharmacokinetic properties*).

Method of administration
Tablets for oral administration.

4.3 Contraindications

Hypersensitivity to pizotifen or to any of the excipients listed in section 6.1

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 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 adverse 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 *Undesirable effects*), therefore gradual withdrawal is recommended.

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

4.5 Interaction with other medicines 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

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Pizotifen may cause sedation, somnolence and dizziness. Therefore, caution should be exercised when driving or using machines. Patients being treated with Sandomigran 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. Tabulate Summary of adverse reactions

Immune system disorders		
	Rare:	Hypersensitivity, face oedema
Metabolism and nutrition disorders		
	Very common:	Increased appetite and body 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:	Convulsions
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 *Special warnings and precautions for use*).
Withdrawal symptoms may include: depression, tremor, nausea, anxiety, malaise, dizziness, sleep disorder and weight decreased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting (New Zealand)

4.9 Overdose

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or the National Poison Centre on 0800 POISON (0800764766) in New Zealand.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimigraine drug, ATC code: N02C X01

Mechanism of action
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.

Pizotifen also possesses appetite-stimulating properties.

Clinical efficacy and safety
Sandomigran is an established product. There are no recent clinical data regarding the approved indications for Sandomigran.

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 was 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 1 mg 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 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 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 faeces. The remaining fraction of the administered dose (about 55 %) is primarily eliminated in the form of metabolites in the urine. Less than 1 % of the administered dose of pizotifen is excreted unchanged through the kidneys, whereas 55 % is excreted as metabolites. 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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: magnesium stearate; talc; povidone; maize starch; lactose, monohydrate.
Coating: titanium dioxide (E171); silica, colloidal anhydrous; acacia; talc, sucrose, cetyl palmitate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C. Protect from light.
Sandomigran must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Sandomigran coated tablets are available in PVC/PVDC blister packs containing 100 tablets and plastic bottle containing 100 tablets.

6.6 Special precautions for disposal

Not applicable

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Australia
AFT Pharmaceuticals Pty Ltd
113 Wicks Road
North Ryde
NSW 2113
Phone: 1800 238 74276

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9. DATE OF FIRST APPROVAL

11/2/1970

10. DATE OF REVISION OF THE TEXT

21/06/2019

Summary table of changes

Section change	Summary of new information
1	Change from 0.5 mg to 500 micrograms
2	Change of metric units and more accurate rounding
4.8	Addition of Australian number
4.9	Addition of Australian number
8	Addition of Australian sponsor
6.5	Addition of package