SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pizotifen 0.5mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.725mg pizotifen malate, equivalent to 0.5mg of pizotifen base.

Excipients with known effect:

Each tablet contains 32.14mg Lactose monohydrate For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

The tablets, which are white, are marked P on one side, plain on reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylactic treatment of recurrent vascular headaches, including classical migraine, common migraine and cluster headache (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

Posology

Adults:

Usually 1.5mg daily, at night or in 3 divided doses. Dosage should be adjusted according to need, up to a maximum of 4.5mg daily. Up to 3mg can be given as a single dose.

Paediatric population (Aged 2 years and over):

Up to 1.5mg daily. This must be given as two or three smaller doses. Do not give children more than 1.0 mg in a single dose.

Elderly:

As for adults.

Clinical work with this product 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

Hypersensitivity to the drug or to any of the other tablet ingredients (see section 6.1. List of excipients).

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.

Although the anticholinergic activity of Pizotifen 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 required in patients with renal insufficiency.

Pizotifen should be used with caution in patients with a history of epilepsy.
Pizotifen coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 cannot be excluded.

Central nervous system agents
The central effects of sedatives, hypnotics, antihistamines (including certain common cold preparations) and alcohol may be enhanced by pizotifen
Pizotifen 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 pizotifen are very limited, it should only be administered during pregnancy 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, 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 Central Nervous System (CNS) effects. Therefore, caution should be exercised when driving or using machines.

Patients being treated with Pizotifen 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 commonly reported 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), including isolated reports; not known (frequency cannot be estimated from the available data).

Immune system disorders:
Rare: Hypersensitivity reactions, face oedema

Skin and Subcutaneous tissues disorders
Rare: urticaria, rash

Metabolism and nutrition disorders:
Very common: Appetite stimulating effect and increase in body weight

Psychiatric disorders:
Rare: Depression, CNS stimulation (e.g. aggression, agitation), hallucination, insomnia and anxiety

Nervous system disorders:
Common: Drowsiness (including somnolence), dizziness
Rare: Paraesthesia
Very rare: Seizures

Gastrointestinal disorders:

Common: Nausea, dry mouth
Uncommon: Constipation

Hepatobiliary disorders
Unknown: Hepatic enzyme increased, jaundice, hepatitis[*1]

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
Acute 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 include depression, malaise, dizziness, sleep disorder weight decrease, anxiety, tremors, insomnia, nausea, and loss of consciousness.

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 and diuresis 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimigraine drug, ATC code: N02C X01
Studies in experimental animals have indicated that pizotifen has a strong anti- serotonin and anti-tryptaminic properties, marked antihistaminic 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 pizotifen in migraine is associated with its ability to modify the humoral mechanism 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 bioavailability 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

Tablet core
Lactose monohydrate
Cellulose microcrystalline
Maize starch
Povidone K30
Magnesium stearate
Silicon dioxide
Tablet film-coating
Hypromellose
Macrogol 6000
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original packaging. Keep in the outer carton.

6.5 Nature and contents of container
White opaque blister, 250 □m PVC/40 gm^2 PVDC sealed to 25 □m aluminium foil/PVDC.

The blistered product is available in cartons containing 28, 30, 56, 60, 84, 90, 112 and 120 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited, 2nd Floor, Connect 38, 1 Dover Place, Ashford, Kent, England, TN23 1FB.

8 MARKETING AUTHORISATION NUMBER(S)
PL 51463/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/11/2009

10 DATE OF REVISION OF THE TEXT
19th June 2025