

**PIZOTIFEN 0.5MG TABLETS (PL 16363/0007)**

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**UKPAR**

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**PIZOTIFEN 0.5MG TABLETS (PL 16363/0007)**

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**LAY SUMMARY**

On 22<sup>nd</sup> November 2007, the MHRA granted Milpharm Limited Marketing Authorisations (licences) for the medicinal products Pizotifen 0.5mg and 1.5mg Tablets (PL 16363/0007-8). These are prescription-only medicines (POM) for the prevention of recurrent migraine headaches.

Pizotifen 0.5mg and 1.5mg Tablets contain the active ingredient pizotifen hydrogen maleate, which belongs to a group of medicines known as antiserotonins. These medicines work by blocking chemicals that act on blood vessels in the brain.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Pizotifen 0.5mg and 1.5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Pizotifen 0.5mg and 1.5mg Tablets (PL 16363/0007-8) on 22<sup>nd</sup> November 2007 to Milpharm Limited.

These are applications for two strengths of Pizotifen Tablets, submitted as generic applications according to Article 10(1) of Directive 2001/83/EC. They cross-refer to the reference products Sanomigran Tablets 0.5mg and 1.5mg, which were originally licensed to Sandoz, but are currently with Novartis. The reference products were originally granted in March 1974, fulfilling the 10-year rule.

The products contain the active ingredient pizotifen hydrogen maleate, an antiserotonin (serotonin antagonist) acting mainly on 5-HT<sub>1</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. It also has some activity as an antihistamine.

Pizotifen 0.5mg and 1.5mg Tablets are indicated for the prophylactic treatment of recurrent vascular headaches, including classical migraine, common migraine and cluster headache (periodic migrainous neuralgia).

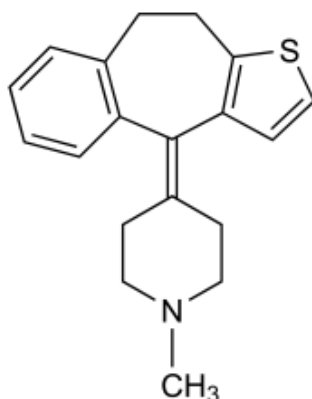
## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### Pizotifen hydrogen malate

INN: Pizotifen hydrogen maleate  
Chemical name: 4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo-  
[4,5(cyclohepta[1,2-b( thiophene hydrogen malate

Structure:



CAS registry number: 15574-96-6

Physical form: White or slightly yellowish white, crystalline powder, odourless or almost odourless.

Molecular formula:  $C_{19}H_{21}NS$ ,  $C_4H_6O_5$

Molecular weight: 429.54

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance pizotifen hydrogen maleate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

The drug substance is packed in polyethylene bottles, which are placed in fibre drums. Satisfactory specifications have been provided for all packaging. Confirmation has been provided that the polyethylene bottles are suitable for the packaging of food and comply with relevant European Pharmacopoeial requirements.

Appropriate stability data have been generated supporting a shelf life of 60 months, when stored at room temperature, in an airtight container and protected from light.

**DRUG PRODUCT****Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, maize starch, povidone K30, magnesium stearate, silicon dioxide, water purified, hydroxypropylmethylcellulose, polyethylene glycol, talc, titanium dioxide and water purified. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. An assurance has been provided that the lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption, using calf rennet.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Product development**

The applicant has provided a suitable product development rationale and data.

Satisfactory assay, impurity and dissolution data have been provided, showing that the proposed products are comparable to the originator products.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. Satisfactory batch formulae have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results appear satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The product is packaged in polyvinylchloride/aluminium/polyvinylidene chloride blisters, which are stored in cardboard boxes. Batch size is 60 tablets for the 0.5mg strength and 28 tablets for the 1.5mg strength. Satisfactory specifications and certificates of analysis for all packaging have been provided.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 48 months has been set with the precautions 'Protect from light', 'Store below 25°C' and 'Store in original container'. These are satisfactory.

**Bioequivalence**

See Clinical Assessment.

**ADMINISTRATIVE**

**Expert Report**

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**

The proposed SPC is pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**

The PIL is pharmaceutically satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

**Labels**

The labels are pharmaceutically satisfactory.

**MAA Forms**

These are satisfactory.

**CONCLUSION**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution, impurity and assay profiles have been demonstrated for the proposed and reference products.

## **PRECLINICAL ASSESSMENT**

These applications for generic products claim essential similarity to Sanomigran Tablets 0.5mg and 1.5mg (Novartis, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been provided with these applications and none are required for applications of this type.



## CLINICAL ASSESSMENT

### CLINICAL PHARMACOLOGY

The applicant has submitted data from a single comparative bioequivalence study. The study was a single-dose, randomised, two-way, crossover study in healthy fasted volunteers comparing the proposed Pizotifen 1.5mg Tablets versus the UK reference product Sanomigran Tablets 1.5mg (Novartis, UK).

Blood samples were taken pre- and up to 72 hours post dose, with a 14-day washout period between doses. Pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ) were determined and 90% confidence intervals calculated for AUC and  $C_{max}$ . The results of these are summarised below:

Parameters	Pizotifen E.P. (mean ± S.D.)	Sanomigran (mean ± S.D.)	Ratio test/ref (%)	90% CI
$C_{max}$ (ng/ml)	8.625 ± 1.496	8.685 ± 1.503	99.3	91.1 – 108.3
$T_{max}$ (h)	2.52 ± 0.98	2.75 ± 1.50	-	-
$AUC_{0-t}$ (ng/ml*h)	111.451 ± 10.605	105.866 ± 7.681	-	-
$AUC_{0-\infty}$ (ng/ml*h)	122.088 ± 11.817	116.998 ± 9.018	104.3	99.9 – 108.7

The 90% confidence limits are within the 80% to 125% range, so bioequivalence can be accepted. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1.5mg strength can be extrapolated to the 0.5mg strength tablets.

### EFFICACY

No new data have been provided.

### SAFETY

No new data have been provided.

### EXPERT REPORTS

The expert report is written by an appropriately qualified Doctor.

### SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with those for the reference products and are satisfactory.

### PATIENT INFORMATION LEAFLET (PIL)

This is consistent with the SPC and is satisfactory.

### LABELLING

These are satisfactory.

### APPLICATION FORM (MAA)

This is clinically satisfactory.

## **DISCUSSION**

The applicant has satisfactorily demonstrated bioequivalence between the 1.5mg strengths of test and originator products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1.5mg strength can be extrapolated to the 0.5mg strength tablets.

## **MEDICAL CONCLUSION**

It is recommended that Marketing Authorisations are granted for these applications.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Pizotifen 0.5mg and 1.5mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

### EFFICACY

Bioequivalence has been demonstrated between the applicant's Pizotifen 1.5mg Tablets and the reference product Sanomigran Tablets 1.5mg (Novartis, UK). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1.5mg strength can be extrapolated to the 0.5mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Sanomigran Tablets.

### RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with pizotifen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**PIZOTIFEN 0.5MG TABLETS (PL 16363/0007)****PIZOTIFEN 1.5MG TABLETS (PL 16363/0008)****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 9 <sup>th</sup> November 2001
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10 <sup>th</sup> December 2001
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 11 <sup>th</sup> January 2002 and 23 <sup>rd</sup> April 2002 and 29 <sup>th</sup> May 2002, and further information relating to the quality dossiers on 15 <sup>th</sup> July 2002, 25 <sup>th</sup> February 2005 and 12 <sup>th</sup> September 2005.
4	The applicant responded to the MHRA's requests, providing further information on 23 <sup>rd</sup> April 2002, 27 <sup>th</sup> May 2002, 30 <sup>th</sup> May 2002 and 12 <sup>th</sup> July 2002 for the clinical sections, and on 13 <sup>th</sup> August 2002, 11 <sup>th</sup> March 2005 and 16 <sup>th</sup> September 2007 for the quality sections.
5	The applications were determined on 14 <sup>th</sup> November 2007

**PIZOTIFEN 0.5MG TABLETS (PL 16363/0007)****PIZOTIFEN 1.5MG TABLETS (PL 16363/0008)****STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Pizotifen 0.5mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.725mg Pizotifen hydrogen malate equivalent to 0.5mg Pizotifen base

For excipients; see section 6.1

### 3 PHARMACEUTICAL FORM

Film coated tablets

White coloured film-coated tablets with P05 embossed on one side.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

#### 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:* Up to 1.5 mg daily in divided dose. Use of 1.5mg tablets is not recommended. The appropriate paediatric doses may be given using 0.5mg tablets. Although up to 1mg has been given as a single dose at night.

*Use in Elderly:* Clinical work has not shown elderly patients to require different dosage from younger patients.

#### 4.3 Contraindications

Known hypersensitivity to pizotifen or any of the excipient used in formulation.

#### 4.4 Special warnings and precautions for use

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 necessary in patients with kidney insufficiency.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### 4.5 Interaction with other medicinal products and other forms of interaction

The central effects of sedatives, hypnotics, antihistamines (including certain common cold preparations) and alcohol may be enhanced by pizotifen.

#### 4.6 Pregnancy and lactation

As clinical data in pregnancy is very limited, it should only be administered under compelling circumstances.

Although the concentration of pizotifen in milk is not likely to affect the infants, its use in nursing mothers is not recommended.

#### 4.7 Effects on ability to drive and use machines

Patients should be cautioned about the possibility of drowsiness and informed of its significance in the driving of vehicles and the operation of machinery.

#### 4.8 Undesirable effects

The most commonly occurring side-effects are drowsiness and an increased appetite, which may lead to an increase in body weight. Other side effects such as dizziness, dry mouth,

nausea and constipation have been reported infrequently. Rare instances of sleep disorders, depression and other mood disturbances have occurred. In children CNS stimulation may occur.

#### **4.9 Overdose**

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

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

### **5 PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

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 pizotifen in migraine is associated with its ability to modify 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**

The absorption of pizotifen is fast (absorption half-life 0.5 to 0.8 hours) and nearly complete (80%). Pizotifen is metabolised with a half-life of about 1hour. The main metabolite (N-glucuronide) is eliminated with a half-life of approximately 23 hours. Protein binding amounts to about 91% and distribution volume is 485 litres. Less than 1% of the administered dose is excreted unchanged in the urine, whereas 55% is excreted as metabolites.

#### **5.3 Preclinical safety data**

None stated

### **6 PHARMACEUTICAL PARTICULARS**

#### **6.1 List of excipients**

Lactose monohydrate  
Microcrystalline cellulose (E460)  
Maize starch  
Povidone K-30 (E1201)  
Magnesium stearate (E572)  
Colloidal silicon dioxide (E551)  
Hypromellose (E464)  
Polyethylene glycol  
Talc (E553b)  
Titanium dioxide (E 171)

#### **6.2 Incompatibilities**

None

#### **6.3 Shelf life**

48 months

- 6.4 Special precautions for storage**  
Do not store above 25°C. Protect the tablets from direct light.
- 6.5 Nature and contents of container**  
PVC/PVdC Aluminium blisters in cardboard carton. Each blister contains 10 tablets and there are six blisters per carton.
- 6.6 Special precautions for disposal and handling**  
None
- 7 MARKETING AUTHORISATION HOLDER**  
Milpharm Limited,  
Ares,  
Odyssey Business Park,  
West End Road,  
South Ruislip HA4 6QD,  
United Kingdom
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 16363/0007
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
21/11/2007
- 10 DATE OF REVISION OF THE TEXT**  
21/11/2007
- 11 DOSIMETRY (IF APPLICABLE)**
- 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**



**1 NAME OF THE MEDICINAL PRODUCT**

Pizotifen 1.5mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 2.175mg Pizotifen hydrogen malate equivalent to 1.5mg Pizotifen base. For excipients; see section 6.1

**3 PHARMACEUTICAL FORM**

Film coated tablets

White coloured film-coated tablets with P15 embossed on one side.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

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

**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.

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The most commonly occurring side-effects are drowsiness and an increased appetite, which may lead to an increase in body weight. Other side effects such as dizziness, dry mouth, nausea and constipation have been reported infrequently. Rare instances of sleep disorders,

depression and other mood disturbances have occurred. In children CNS stimulation may occur.

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None stated

## **6 PHARMACEUTICAL PARTICULARS**

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Magnesium stearate (E572)  
Colloidal silicon dioxide (E551)  
Hypromellose (E464)  
Polyethylene glycol  
Talc (E553b)  
Titanium dioxide (E 171)

### **6.2 Incompatibilities**

None

### **6.3 Shelf life**

48 months

- 6.4 Special precautions for storage**  
Do not store above 25°C. Protect the tablets from direct light.
- 6.5 Nature and contents of container**  
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