Public Assessment Report

UKPAR

Betahistine Dihydrochloride 8mg Tablets
Betahistine Dihydrochloride 16mg Tablets

(Betahistine dihydrochloride)

UK Licence No: PL 43461/0049-0050

Flamingo Pharma (UK) Ltd.
LAY SUMMARY

Betahistine Dihydrochloride 8mg Tablets
Betahistine Dihydrochloride 16mg Tablets

(Betahistine dihydrochloride)

This is a summary of the Public Assessment Report (PAR) for Betahistine Dihydrochloride 8mg Tablets (PL 43461/0049) and Betahistine Dihydrochloride 16mg Tablets (PL 43461/0050). It explains how Betahistine Dihydrochloride 8mg and 16mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Betahistine Dihydrochloride 8mg and 16mg Tablets.

For practical information about using Betahistine Dihydrochloride 8mg and 16mg Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Betahistine Dihydrochloride 8mg and 16mg Tablets and what are they used for?
This medicine is used to treat vertigo, tinnitus (ringing in the ears) and hearing loss associated with Ménière's disease.

These applications are the same as Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004) which are already authorised.

The company (RI Pharma Limited) that makes Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004) has agreed that its scientific data can be used as a basis for the grant of identical licences for Betahistine Dihydrochloride 8mg and 16mg Tablets.

How do Betahistine Dihydrochloride 8mg and 16mg Tablets work?
This medicine contains the active ingredient betahistine dihydrochloride which works by reducing the pressure in the inner ear.

How are Betahistine Dihydrochloride 8mg and 16mg Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient should always use this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

Swallow the tablets with water and always take with or after a meal.

Usual dose for adults and the elderly:
The usual starting dose is 16 mg of betahistine hydrochloride three times a day. The patient’s doctor may change the dose to between 24 and 48 mg a day after the patient has been taking treatment for a while.

This medicine can only be obtained with a prescription.

For further information on how Betahistine Dihydrochloride 8mg and 16mg Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Betahistine Dihydrochloride 8mg and 16mg Tablets have been shown in studies?
Betahistine Dihydrochloride 8mg and 16mg Tablets are considered identical to previously authorised
Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004) with the same benefits and risks. So, no new studies have been provided for Dihydrochloride 8mg and 16mg Tablets, but reference is made to the studies for Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004).

**What are the possible side effects from Betahistine Dihydrochloride 8mg and 16mg Tablets?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Betahistine Dihydrochloride 8mg and 16mg Tablets are considered to be identical to the previously authorised applications for Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004) with the same benefits and risks.

For a full list of all the side effects reported with Betahistine Dihydrochloride 8mg and 16mg Tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

**Why were Betahistine Dihydrochloride 8mg and 16mg Tablets Approved?**
The MHRA decided that the benefits of Betahistine Dihydrochloride 8mg and 16mg Tablets are greater than the risks and recommended that they are approved for use.

**What measures are being taken to ensure the safe and effective use of Betahistine Dihydrochloride 8mg and 16mg Tablets?**
A Risk Management Plan has been developed to ensure that Betahistine Dihydrochloride 8mg and 16mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Betahistine Dihydrochloride 8mg and 16mg Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Betahistine Dihydrochloride 8mg and 16mg Tablets**
Marketing Authorisations were granted in the UK on 22 March 2018.

The full PAR for Betahistine Dihydrochloride 8mg and 16mg Tablets follows this summary.

For more information about treatment with Betahistine Dihydrochloride 8mg and 16mg Tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in May 2018.
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I INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Flamingo Pharma (UK) Ltd Marketing Authorisations for the medicinal product Betahistine Dihydrochloride 8mg and 16mg Tablets (PL 43461/0049-0050) on 22 March 2018.

This product is a prescription only medicine (POM) and is indicated for the treatment of vertigo, tinnitus and hearing loss associated with Ménière's syndrome.

These applications were submitted as simple abridged (informed consent) applications according to Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to the medicinal products Betahistine Dihydrochloride Tablets 8mg and 16mg which were first authorised to the marketing authorisation holder (MAH) Sanofi Winthrop Limited (PL 11723/0196-0197) on 06 December 1995 and subsequently underwent several changes of ownership procedures of which the most recent was to the current MAH RI Pharma Limited (PL 34976/0003-0004) on 11 September 2009.

The mechanism of action of betahistine is only partly understood. There are several plausible hypotheses that are supported by animal studies and human data:
• Betahistine affects the histaminergic system:
  Betahistine acts both as a partial histamine H1-receptor agonist and histamine H3-receptor antagonist also in neuronal tissue, and has negligible H2-receptor activity. Betahistine increases histamine turnover and release by blocking presynaptic H3-receptors and inducing H3-receptor downregulation.

• Betahistine may increase blood flow to the cochlear region as well as to the whole brain:
  Pharmacological testing in animals has shown that the blood circulation in the striae vascularis of the inner ear improves, probably by means of a relaxation of the precapillary sphincters of the microcirculation of the inner ear. Betahistine was also shown to increase cerebral blood flow in humans.

• Betahistine facilitates vestibular compensation:
  Betahistine accelerates the vestibular recovery after unilateral neurectomy in animals, by promoting and facilitating central vestibular compensation; this effect characterized by an up-regulation of histamine turnover and release, is mediated via the H3 Receptor antagonism. In human subjects, recovery time after vestibular neurectomy was also reduced when treated with betahistine.

• Betahistine alters neuronal firing in the vestibular nuclei:
  Betahistine was also found to have a dose dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei.

No new data were submitted nor were necessary to be submitted for these applications, as the data are identical to the data for the previously granted cross-referenced products.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
II QUALITY ASPECTS

II.1 Introduction
These are abridged applications for Betahistine Dihydrochloride 8mg and 16mg Tablets (PL 43461/0049-0050) submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to the medicinal products Betahistine Dihydrochloride Tablets 8mg and 16mg which were first authorised to the marketing authorisation holder (MAH) Sanofi Winthrop Limited (PL 11723/0196-0197) on 06 December 1995 and subsequently underwent several changes of ownership procedures of which the most recent was to the current MAH RI Pharma Limited (PL 34976/0003-0004) on 11 September 2009. The applications are considered valid.

II.2 Drug Substance

Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3 Medicinal Product

Name
The proposed product names for these applications are Betahistine Dihydrochloride 8mg and 16mg Tablets. The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each tablet contains 8 mg or 16 mg betahistine dihydrochloride. Both strengths of the finished product are packaged into PVC/PE/PVDC with backing of aluminium foil blister packs contained in a cardboard carton in pack sizes of 84, 100 and 120 tablets. Not all pack sizes may be marketed.

The proposed shelf life of the unopened product is 2 years with the storage condition ‘Do not store above 30°C.’

The proposed packaging, shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

Legal status
Prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Flamingo Pharma (UK) Ltd, 1st Floor, Kirkland house, 11-15 Peterborough Road, Harrow, Middlesex, HA1 2AX, United Kingdom

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference products.
Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross-reference products and the maximum batch size is stated.

Finished product/shelf-life specifications
The proposed finished product specifications are in line with the details registered for the cross-reference products.

TSE Compliance
With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Bioequivalence
No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formulae utilising the same processes as the cross-reference products, Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004).

Expert Report
The applicant cross-refer to the data for Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004) to which these applications are claimed to be identical. This is acceptable.

Product Names and Appearance
See Section II.3 ‘Medicinal Product; Name’ for details of the proposed product names. The appearance of the products is identical to that of the cross-reference products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with these applications is acceptable. The grant of Marketing Authorisations is recommended.
II NON-CLINICAL ASPECTS

Introduction
As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

Introduction
As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed and the RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisations and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MHRA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Betahistine Dihydrochloride Tablets 8mg and 16mg (PL 34976/0003-0004). The bridging report submitted by the applicant is acceptable.
VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with betahistine dihydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
Note: Blank area/space for Manufacturing License number & internal foil tracking code.

Note: Batch Number and Expiry will be printed/embossed here during production.
PAR Betaistine Dihydrochloride 8mg and 16mg Tablets

PL 43461/0049-0050

Note:
Blank area/space for Manufacturing License number & internal foil tracking code

Note:
Batch Number and Expiry will be printed/embossed here during production
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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