Public Assessment Report

Betahistine Hydrochloride 8mg Tablets
Betahistine Hydrochloride 16mg Tablets

Betahistine Hydrochloride

PL 08553/0208
PL 08553/0209

Dr Reddy’s Laboratory (UK) Ltd

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>3</td>
</tr>
<tr>
<td>Overall Conclusion And Risk Benefit/Analysis</td>
<td>5</td>
</tr>
<tr>
<td>Steps Taken During Assessment</td>
<td>6</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>7</td>
</tr>
<tr>
<td>Labels and Leaflet</td>
<td>13</td>
</tr>
</tbody>
</table>
Lay Summary

The MHRA today granted Dr Reddy’s Laboratory (UK) Ltd Market Authorisations for the medicinal products Betahistine Hydrochloride 8mg and 16mg Tablets. These are prescription only medicines for the treatment of vertigo, tinnitus and hearing loss associated with Meniere’s syndrome and contain the active ingredient betahistine hydrochloride. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Betahistine Hydrochloride 8mg and 16mg Tablets outweigh the risks hence Marketing Authorisations have been granted.
Scientific Discussion

INTRODUCTION

This Public Assessment Report is based on the National Assessment Report for the recently granted Market Authorisations for Betahistine Hydrochloride 8mg and 16mg Tablets (PL 08553/0208 and PL 08553/0209). These were abridged applications made under Article 10.1c of Directive 2001/83/EC cross-refering to PLs 10622/0048 and 0049 for Betahistine Hydrochloride 8 mg and 16 mg Tablets, respectively, both granted to Pliva Pharma Ltd on 14 June 2000.

A letter of access dated 27 January 2004 has been submitted. Appropriate declarations confirm that the applicant has access to Pre-clinical data and Clinical data and have sufficient Quality data in their possession to support the applications. The proposed finished product manufacturers have confirmed that they are prepared to manufacture the products on the applicant’s behalf. Satisfactory expert statements from pre-clinical, clinical and pharmaceutical experts were provided.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

The proposed drug substance specification is identical to that approved for the cross reference products. The active substance manufacturers are the same as previously authorised for the cross-referenced products.

DRUG PRODUCT

The composition of the drug product is the same as the cross reference product and is listed below.

- Povidone K90
- Microcrystalline cellulose
- α-lactose monohydrate
- Colloidal anhydrous silica
- Crospovidone
- Stearic acid

The formula, reference to standards and modifiers are in line with reference product. A brief description of the manufacturing method was provided. A statement from the pharmaceutical expert indicates that an identical manufacturing process to that for the cross-reference product is used. Applicant has provided the details for the manufacturing approvals previously granted.

A satisfactory current TSE certificate and declaration from the lactose supplier was provided. None of the ingredients comes from a genetically modified organism. Satisfactory manufacturing authorisations and GMP certificates were also provided. The container closure system was found to be satisfactory.
PRODUCT LITERATURE

Minor changes to the SPC were made to bring it in line with the reference product and subsequent minor changes were made to the Patient Information Leaflet.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
Marketing Authorisations were granted.

PRE-CLINICAL ASSESSMENT
No pre-clinical assessment was necessary for this application

MEDICAL ASSESSMENT

No medical assessment was necessary for this application.
Overall Conclusion and Risk/Benefit Analysis

Quality

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

Pre-Clinical

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

Clinical

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

Risk/Benefit Analysis

The quality of the products, Betahistine Hydrochloride 8mg and 16mg Tablets, is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. The risk benefit is therefore considered to be positive.
## Steps Taken During Assessment

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 13(^{th}) February 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 2(^{nd}) June 2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 16 March 2005.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 4(^{th}) July 2005.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 3(^{rd}) August 2007.</td>
</tr>
</tbody>
</table>

Jonathan, is the above information accurate? 26 months from receipt to validation of the applications seems excessive. Was the information requested in March 2005 to do with the validation? This may be the case as I think Liz had some applications that were deficient at receipt. If it is the best that we have - then no problem.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Betahistine Hydrochloride 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 8mg Betahistine Hydrochloride
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet
Betahistine Hydrochloride 8mg Tablets are white to almost white, cylindrical, bi-plane tablets imprinted with “B8” on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Vertigo, tinnitus and hearing loss associated with Ménière’s syndrome.

4.2 Posology and method of administration
Adults (including the elderly)
Initially 16mg three times daily, taken preferably with meals. Maintenance doses are generally in the range 24-48mg daily.
Children
No dosage recommendations.

4.3 Contraindications
Phaeochromocytoma.
Hypersensitivity to any component of the product.

4.4 Special warnings and precautions for use
Caution is advised in patients with a history of peptic ulcer. Clinical intolerance to Betahistine hydrochloride in bronchial asthma patients has been shown in a relatively few patients and therefore caution should be exercised when administering betahistine to patients with bronchial asthma. Each 8mg tablet contains 70mg of lactose (as alpha-lactose monohydrate). 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
Although an interaction between Betahistine hydrochloride and antihistamines could theoretically be expected, no such interactions have been reported.

4.6 Pregnancy and lactation
High dosage animal studies have shown no teratogenic properties, but the usual precautions should be observed when administering Betahistine hydrochloride to patients during pregnancy.

4.7 Effects on ability to drive and use machines
Betahistine does not affect driving or psychomotor ability, even at over four times the recommended daily dose.

4.8 Undesirable effects
Relatively few undesirable effects have been reported. These include gastrointestinal upset (including dyspepsia), headache, skin rash and pruritus.

4.9 Overdose
No specific antidote. Gastric lavage and symptomatic treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Betahistine hydrochloride is a specific histamine agonist with virtually no H2-activity. It seems to act on the precapillary sphincter in the stria vascularis of the inner ear, thus reducing the pressure in the endolympathic space.

5.2 Pharmacokinetic properties
Betahistine is rapidly and completely absorbed after oral administration of the drug in tablet form. It is excreted almost quantitatively in urine as 2-pyridylacetic acid for 24 hours following administration. No unchanged Betahistine has been detected.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to information already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Povidone K90
Microcrystalline cellulose
α-lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Stearic acid.

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
36 months.

6.4 **Special precautions for storage**
Do not store above 25°C.
Store in the original package.

6.5 **Nature and contents of container**
Blister strips consisting of 250 μm transparent PVC, a 60 g/m² PVdC layer and 20 μm hard temper aluminium foil, contained in a carton.
Pack size: 120 tablets.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Dr, Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
East Yorkshire
HU17 OLD

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 08553/0208

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
03/08/2007

10 **DATE OF REVISION OF THE TEXT**
03/08/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Betahistine Hydrochloride 16 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 16mg Betahistine Hydrochloride
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablet
Betahistine Hydrochloride 16mg Tablets are white to almost white, cylindrical, bi-plane tablets imprinted with “B16” on one side and scored on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Vertigo, tinnitus and hearing loss associated with Ménière’s syndrome.

4.2 Posology and method of administration
Adults (including the elderly)
Initially 16mg three times daily, taken preferably with meals. Maintenance doses are generally in the range 24-48mg daily.
Children
No dosage recommendations.

4.3 Contraindications
Phaeochromocytoma. Hypersensitivity to any component of the product.

4.4 Special warnings and precautions for use
Caution is advised in patients with a history of peptic ulcer. Clinical intolerance to Betahistine hydrochloride in bronchial asthma patients has been shown in a relatively few patients and therefore caution should be exercised when administering betahistine to patients with bronchial asthma. Each 16 mg tablet contains 140mg of lactose (as alpha-lactose monohydrate). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

UKPAR Dr Reddy’s Laboratories (UK) Ltd, Betahistine Hydrochloride 8mg and 16mg Tablets
4.5 **Interaction with other medicinal products and other forms of interaction**
Although an interaction between Betahistine hydrochloride and antihistamines could theoretically be expected, no such interactions have been reported.

4.6 **Pregnancy and lactation**
High dosage animal studies have shown no teratogenic properties, but the usual precautions should be observed when administering Betahistine hydrochloride to patients during pregnancy.

4.7 **Effects on ability to drive and use machines**
Betahistine does not affect driving or psychomotor ability, even at over four times the recommended daily dose.

4.8 **Undesirable effects**
Relatively few undesirable effects have been reported. These include gastrointestinal upset (including dyspepsia), headache, skin rash and pruritus.

4.9 **Overdose**
No specific antidote. Gastric lavage and symptomatic treatment is recommended.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Betahistine hydrochloride is a specific histamine agonist with virtually no H2-activity. It seems to act on the precapillary sphincter in the stria vascularis of the inner ear, thus reducing the pressure in the endolymphatic space.

5.2 **Pharmacokinetic properties**
Betahistine is rapidly and completely absorbed after oral administration of the drug in tablet form. It is excreted almost quantitatively in urine as 2-pyridylacetic acid for 24 hours following administration. No unchanged Betahistine has been detected.

5.3 **Preclinical safety data**
There are no pre-clinical data of relevance to the prescriber which are additional to information already included in other sections of the SPC.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Povidone K90
Microcrystalline cellulose
α-lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Stearic acid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
Blister strips consisting of 250 µm transparent PVC, a 60 g/m² PVdC layer and 20 µm hard temper aluminium foil, contained in a carton.
Pack sizes: 60 and 84 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr, Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
East Yorkshire
HU17 OLD

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0209

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/08/2007

10 DATE OF REVISION OF THE TEXT
03/08/2007
PL 08553/0208-9

Labels and Leaflet

BETAHISTINE HYDROCHLORIDE 8mg TABLETS
BETAHISTINE HYDROCHLORIDE 16mg TABLETS
PATIENT INFORMATION LEAFLET

Please read this leaflet carefully before you start taking this medicine. Keep this leaflet until you have finished the prescribed course of Betahistine Hydrochloride Tablets. You may need to read it again if you have any further questions concerning your medicine ask your doctor or pharmacist for more information.

What you need to know about your tablets
The tablets contain: Betahistine Hydrochloride 8mg Tablets or Betahistine Hydrochloride 16mg Tablets. Each tablet contains either 8mg or 16mg of Betahistine Hydrochloride as the active ingredient.

The tablets also contain: Microcrystalline cellulose, lactose, colloidal anhydrous silica, croscarmellose sodium and steatic acid. Betahistine Hydrochloride 8mg tablets are available in blister packs of 120 tablets. Betahistine Hydrochloride 16mg tablets are available in blister packs of 60 and 84 tablets.

What do the tablets do?
Betahistine Hydrochloride tablets are used to treat vertigo (dizziness), tinnitus (noises in the ear) and hearing loss, when these are associated with Ménière’s syndrome.

How do Betahistine Hydrochloride tablets work?
Betahistine Hydrochloride is a histamine agonist, which means it has a similar structure and action to histamine, a chemical which is found naturally in the body. Histamine is thought to be involved in the dilation of blood vessels in the body and contraction of smooth muscle. Ménière’s syndrome is a condition which is thought to be caused by the pressure of excess fluid in the ear. Betahistine seems to act on the smooth muscle surrounding the blood vessels of the middle ear, and to improve blood flow, thus reducing the pressure within the ear.

Before taking your medicine
Before taking the medicine, tell your doctor if you have ever had any unusual or allergic reactions to Betahistine Hydrochloride or to any of the other ingredients listed above.

It is important that your doctor is aware of any other medication you are taking whether prescribed or not. Make sure to tell your doctor or pharmacist if you have any other medical problems.

Ask yourself the following questions:
- Do you suffer from a condition called phaeochromocytoma (high blood pressure due to a tumor near the kidney)?
- Do you have peptic ulcers?
- Do you suffer from bronchial asthma?
- Are you pregnant or do you think you may be pregnant?

If the answer to any of these questions is YES, tell your doctor or pharmacist as soon as possible and before taking any tablets.

Use in pregnancy
Do not use Betahistine Hydrochloride if you are pregnant, or likely to become pregnant. Tell your doctor or pharmacist if you are breast-feeding.

Can you take Betahistine Hydrochloride Tablets with other medicines?
You can take these tablets with other medicines, but there may be some medicines which can interfere with Betahistine Hydrochloride. It is very important that your doctor or pharmacist know all the medicines which you are taking, whether or not any medicines were prescribed by your doctor or bought without a prescription from the pharmacy or elsewhere.

Special precautions and warnings
Each 8mg tablet contains 70mg of lactose, and each 16mg tablet contains 140mg of lactose (as alpha-lactose monohydrate). Lactose is a sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Taking your medicine
It is important to take the tablets as directed by your doctor. If you are not sure, ask your doctor or pharmacist. Swallow the tablets whole with a drink of water, preferably a meal. Do not chew the tablets. Do not exceed this dose.

Adults: Initially 16mg three times daily. Your doctor may then adjust your dose to between 24 and 48mg daily.

Children: There are no dosage recommendations made for children.

After taking your medicine
It is important to keep the dose on the label of your medicine. Taking more tablets than this is unlikely to be dangerous unless many are taken at once. In that case, or if you think a child has swallowed any, contact your doctor or nearest hospital casualty department immediately. Take with you any remaining tablets or packaging so that they can be identified.

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not double the dose, just carry on as before.

If after taking your medicine you have any problems consult your doctor.

Side effects
Like all medicines, Betahistine Hydrochloride tablets may have side effects. Most adverse effects are generally minor and do not normally interfere with treatment. These may include: gastro-intestinal upset (including dyspepsia - indigestion or upset stomach), headache, skin rash and pruritus (itching of the skin).

Tell your doctor if any of the above symptoms persist, or if any other symptoms not mentioned above which become troublesome during treatment.

Storing your medicine
Do not store above 25°C. Store in the original package.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

On the packaging you will find a printed expiry date. This is the date when the medicine is no longer fit for use. Do not use Betahistine Hydrochloride tablets after this date. If you have any tablets which are out of date, return them to your pharmacist for disposal.

A reminder
Remember this medicine is for you. Never give it to someone else, even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist who have access to additional information.

Date of preparation: 13.03.2006
Betahistine Hydrochloride 8mg Tablets, PL8553/0208
Betahistine Hydrochloride 16mg Tablets, PL8553/0209
Dr. Reddy’s Laboratories (UK) Limited
BH10 2P1

UKPAR Dr Reddy’s Laboratories (UK) Ltd, Betahistine Hydrochloride 8mg and 16mg Tablets 13
UKPAR Dr Reddy’s Laboratories (UK) Ltd, Betahistine Hydrochloride 8mg and 16mg Tablets
Each tablet contains 16 milligrams (mg) of Betahistine Hydrochloride. Also contains lactose.

For oral use. Dosage: Use as directed by your doctor. Please read the enclosed leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C.

Store in the original package.

PL 08553/0209
Dr. Reddy's Laboratories (UK) Limited, 6 Riverview Road, Beverley, East Riding of Yorkshire HU17 0LD, UK.
UKPAR Dr Reddy’s Laboratories (UK) Ltd, Betahistine Hydrochloride 8mg and 16mg Tablets