Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Betahistine Dihydrochloride DAWA 8mg Tablets

Betahistine Dihydrochloride DAWA 16mg Tablets

Betahistine Dihydrochloride DAWA 24mg Tablets

betahistine dihydrochloride

PL 30684/0297-0299

DAWA Limited

LAY SUMMARY

Betahistine Dihydrochloride DAWA 8, 16 and 24mg Tablets
betahistine dihydrochloride

This is a summary of the Public Assessment Report (PAR) for Betahistine Dihydrochloride DAWA 8, 16 and 24mg Tablets. It explains how these products were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Betahistine in this lay summary for ease of reading.

For practical information about using Betahistine, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Betahistine and what is it used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Serc®-8, Serc®-16 and Betaserc 24 mg Tablets.

Betahistine tablets contains betahistine dihydrochloride. This medicine is called a histamine analogue.

Betahistine is used for Ménière's disease. The signs of this include:
- dizziness (vertigo)
- ringing in the ears (tinnitus)
- hearing loss or hearing difficulty

How does Betahistine work?
This medicine works by improving blood flow in the inner ear. This lowers the build-up of pressure, but precisely how this medicine works is not yet fully understood.

How is Betahistine used?
The pharmaceutical form of these medicines is tablets and the route of administration is by mouth (oral).

How Betahistine is taken
The tablets should be swallowed with water and should be taken with or after a meal.
Betahistine can cause mild stomach problems. However, if Betahistine is taken with food this may help reduce the chances of stomach problems.

How much Betahistine to take
Betahistine is not recommended for those under 18 years old.

The recommended dose is:
Adults
- The recommended dose is 24 mg to 48 mg per day.
- If a high daily maintenance dose is needed, the 24 mg tablet strength can be taken 2 times a day (1 tablet in the morning and evening).
- The daily dose should not exceed 48 mg.

- If the patient takes more than one tablet each day, the tablets should be spread evenly over the day. For example, the patient should take one tablet in the morning, one at midday and one in the evening.
- The patient should try to take their tablet at the same time each day. This will make sure that there is a steady amount of the medicine in entering the body.
- Taking this medicine at the same time will also help the patient to remember to take their tablets.

This medicine can take a while to start to work. The patient should continue to take this medicine, even if its effects are not noticed.

For further information on how Betahistine are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

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

What benefits of Betahistine have been shown in studies?
Because Betahistine are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Betahistine?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Betahistine are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Betahistine approved?
It was concluded that, Betahistine has been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Betahistine?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Betahistine. The RMP details the important risks of Betahistine, how these risks can be minimised, any uncertainties about Betahistine (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Betahistine:
Important identified risks:

- Hypersensitivity reactions (including anaphylaxis)

Important potential risks:

- None

Missing information:

- Use in paediatric population (<18years of age)
- Use in pregnancy and lactation.

The information included in the SmPCs and the PIL are compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Betahistine are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Betahistine
Marketing authorisations for Betahistine were granted in the United Kingdom on 11 July 2022.

The full PAR for Betahistine follows this summary.

This summary was last updated in November 2022.

TABLE OF CONTENTS

I INTRODUCTION 6
II QUALITY ASPECTS 7
III NON-CLINICAL ASPECTS 8
IV CLINICAL ASPECTS 9
V USER CONSULTATION 10
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION 10
TABLE OF CONTENT OF THE PAR UPDATE 13

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Betahistine Dihydrochloride DAWA 8, 16 and 24mg Tablets (PL 30684/0297-0299) could be approved.

The products are approved for the following indication:

Vertigo, tinnitus and hearing loss associated with Ménière's syndrome.

The mechanism of action of betahistine is only partly understood. There are several plausible hypotheses that are supported by animal studies and human data. Please refer to Section 5.1 of the Summary of Product Characteristics for further information, this document is available on the MHRA products website.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products Serc®-8, Serc®-16 and Betaserc 24 mg Tablets, that have been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

Advice was sought from the Commission of Human Medicines (CHM) on 23 May 2019. Following provision of additional data related to bioequivalence the CHM were reassured of the bioequivalence of Betahistine Dihydrochloride DAWA 8, 16 and 24mg Tablets to the reference medicines.

The MHRA has been assured, that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Betahistine were granted in the United Kingdom (UK) on 11 July 2022.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 8 mg, 16 mg or 24 mg of betahistine dihydrochloride. The tablets also contain citric acid anhydrous, microcrystalline cellulose, mannitol (E421), silica colloidal anhydrous, and purified talc.

The finished products are packaged in Alu/PVC/ACLAR blister packs containing 84 or 120 tablets, or Alu/PVC/PVDC blister packs containing 84 or 120 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

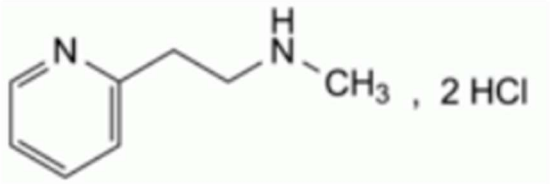
II.2 ACTIVE SUBSTANCE

rINN: betahistine dihydrochloride

Chemical Name: *N*-Methyl-2-(pyridin-2-yl)ethanamine dihydrochloride

Molecular Formula: $C_8H_{14}Cl_2N_2$

Chemical Structure:



Molecular Weight: 209.1

Appearance: White or slightly yellow powder, very hygroscopic.

Solubility: Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in 2-propanol.

Betahistine dihydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT(S)

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, without special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of betahistine dihydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic version of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of betahistine dihydrochloride are well-known. With the exception of data from a bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

An open-label, balanced, randomised, single dose, two-treatment, two-sequence, two-period, cross over, oral bioequivalence study comparing Betahistine Dihydrochloride 24mg Tablets versus the reference product Betaser*c*® 24mg Tablets in healthy, adult, human subjects under fasting condition.

In each study period, after an overnight fast of at least 10 hours, subjects were administered with either a single dose of the reference product or test product. Blood samples were taken pre-dose and up to 30 hours post dose, with a washout period of 3 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	90 % Confidence Intervals (%)	CV(%)[1]
Ln (C_{max}) (ng/ml)	103.38	98.06 - 108.98	10.68
Ln (AUC_{0-t}) (hr *ng/ml)	107.05	104.22 - 109.97	5.42

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product (8 and 16 mg) meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 24 mg strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine

pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

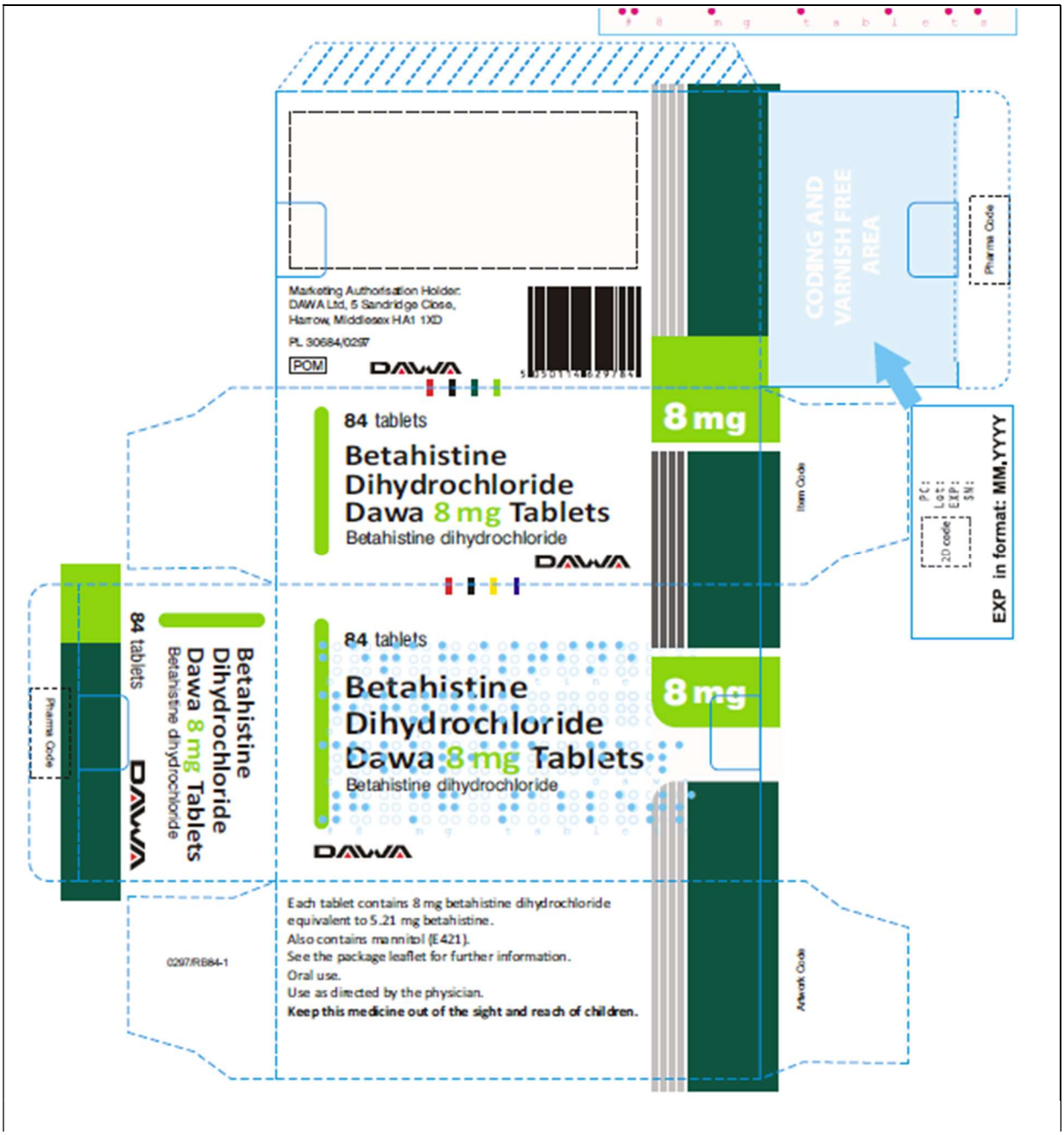
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with betahistine dihydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Marketing Authorisation Holder:
DAWA Ltd, 5 Sandridge Close,
Harrow, Middlesex HA1 1XD
PL 30684/0297
POM
DAWA
84 tablets
Betahistine Dihydrochloride Dawa 8 mg Tablets
Betahistine dihydrochloride
8 mg
CODING AND VARNISH FREE AREA
Pharma Code
Item Code
EXP in format: MM,YYYY
Each tablet contains 8 mg betahistine dihydrochloride equivalent to 5.21 mg betahistine.
Also contains mannitol (E421).
See the package leaflet for further information.
Oral use.
Use as directed by the physician.
Keep this medicine out of the sight and reach of children.
0297/RB84-1
Artwork Code

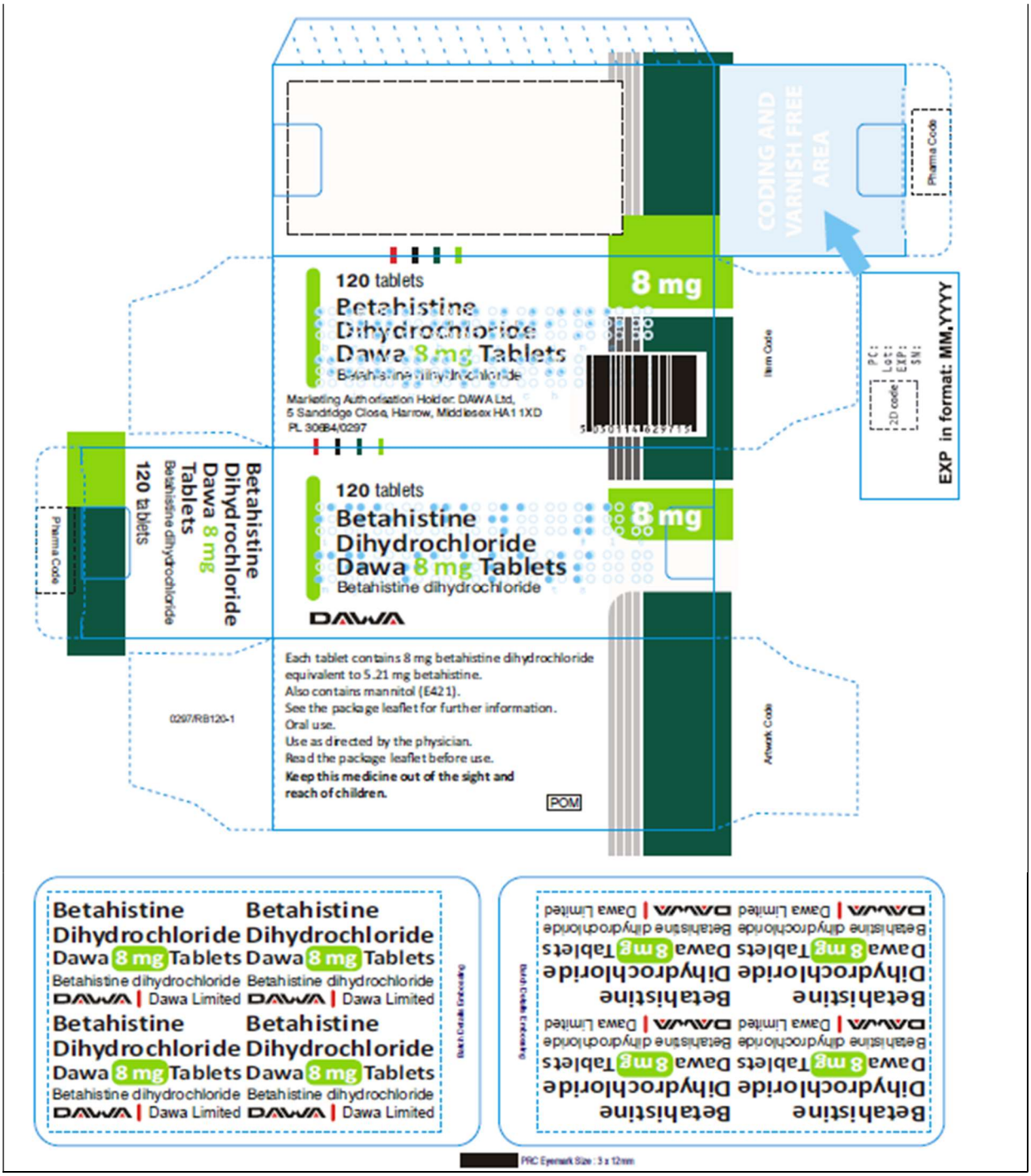

CODING AND VARNISH FREE AREA
Pharma Code
EXP in format: MM,YYYY
PC:
Lot:
2D code
EXP:
SN:
Item Code
120 tablets
Betahistine Dihydrochloride Dawa 8 mg Tablets
Betahistine dihydrochloride
8 mg
Marketing Authorisation Holder: DAWA Ltd,
5 Sandridge Close, Harrow, Middlesex HA1 1XD
PL 30684/0297
Each tablet contains 8 mg betahistine dihydrochloride equivalent to 5.21 mg betahistine.
Also contains mannitol (E421).
See the package leaflet for further information.
Oral use.
Use as directed by the physician.
Read the package leaflet before use.
Keep this medicine out of the sight and reach of children.
POM
0297/RB120-1
Artwork Code
DAWA
Dawa Limited
Batch Details Embossing
PRC Eyemark Size : 3 x 12mm

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N