Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Desloratadine 5 mg film-coated tablets

(Desloratadine)

Procedure No: UK/H/5815/003/DC

UK Licence Number: PL 17907/0501

Bristol Laboratories Ltd.

LAY SUMMARY

Desloratadine 5 mg film-coated tablets

(desloratadine, tablet, 5 mg)

This is a summary of the Public Assessment Report (PAR) for Desloratadine 5 mg film-coated tablets (PL 17907/0501; UK/H/5815/003/DC). It explains how Desloratadine 5 mg film-coated tablets were assessed and their authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Desloratadine 5 mg film-coated tablets.

The product will be referred to as Desloratadine tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Desloratadine tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Desloratadine tablets and what are they used for?
Desloratadine tablets are a 'generic medicine'. This means that Desloratadine tablets are similar a 'reference medicine' already authorised in the European Union (EU) called Aerius 5 mg film-coated tablets, which were centrally authorised to Schering Plough Europe on 15 January 2001.

This medicine relieves symptoms associated with allergic rhinitis (inflammation of the nasal passages caused by an allergy, for example, hay fever or allergy to dust mites) in adults and adolescents 12 years of age and older. These symptoms include sneezing, runny or itchy nose, itchy palate, and itchy, red or watery eyes.

Desloratadine tablets are also used to relieve the symptoms associated with urticaria (a skin condition caused by an allergy). These symptoms include itching and hives.

Relief of these symptoms lasts a full day and helps the patient to resume their normal daily activities and sleep.

How do Desloratadine tablets work?
This medicine contains the active substance, desloratadine, which is an antihistamine that does not cause drowsiness. It helps to control the patient's allergic reaction and its symptoms.

How are Desloratadine tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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

Adults and adolescents 12 years of age and over
The recommended dose is one tablet once a day with or without food.

This medicine is for oral use.

Regarding the duration of treatment, the patient's physician will determine the type of allergic rhinitis they are suffering from and will determine for how long the patient should take this medicine.

If the patient's allergic rhinitis is intermittent (presence of symptoms for less than 4 days per week or for less than 4 weeks), their physician will recommend them a treatment schedule that will depend on the evaluation of the history of their disease.

If the patient's allergic rhinitis is persistent (presence of symptoms for 4 days or more per week and for more than 4 weeks), their physician may recommend them a longer term treatment.

For urticaria, the duration of treatment may be variable from patient to patient and therefore the patient should follow the instructions of their physician.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how this medicine is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Desloratadine tablets have been shown in studies?
Because Desloratadine tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Aerius 5 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Desloratadine tablets?
Because Desloratadine tablets are a generic medicine and are bioequivalent to the reference medicine Aerius 5 mg film-coated tablets, its benefits and possible side effects are taken as being the same as the reference medicine.

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

For the full list of all side effects reported with Desloratadine tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Desloratadine tablets approved?
It was concluded that, in accordance with EU requirements, Desloratadine tablets have been shown to have comparable quality and to be bioequivalent to Aerius 5 mg film-coated tablets. Therefore, the MHRA decided that, as for Aerius 5 mg film-coated tablets; the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Desloratadine tablets?
A risk management plan (RMP) has been developed to ensure that Desloratadine tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Desloratadine 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 Desloratadine tablets

Spain, Germany and the UK agreed to grant Marketing Authorisations for Desloratadine tablets on 07 March 2016. Marketing Authorisations were granted in the UK on 05 April 2016.

The full PAR for Desloratadine tablets follows this summary.

For more information about treatment with Desloratadine tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Ltd, a marketing authorisation for the medicinal product Desloratadine tablets (PL 17907/0501; UK/H/5815/003/DC) The product is a prescription-only medicine (POM) indicated in adults and adolescents aged 12 years and older for the relief of symptoms associated with:
- allergic rhinitis (see section 5.1 of the SmPC)
- urticaria (see section 5.1 of the SmPC).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain and Germany as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Aerius 5 mg film-coated tablets, which was centrally authorised to Schering Plough Europe on 15 January 2001 and subsequently underwent a change of ownership procedure to the current marketing authorisation holder (MAH) Merck Sharp & Dohme Ltd.

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H1- receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H1-receptors because the substance is excluded from entry to the central nervous system.

Desloratadine has demonstrated antiallergic properties from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.

The applicant submitted one bioequivalence study with their original submission. However, following recent regulatory action, the bioequivalence study that was performed to support this application was not considered suitable. The applicant therefore submitted two new bioequivalence studies to support this application. The applicant has stated that the new bioequivalence studies were conducted in accordance with the current EMA guidance documents, Good Clinical Practice (GCP), as established by the International Conference on Harmonization (ICH), the basic principles defined in Division 5 of the Canadian Food and Drug Regulations, the Belmont Report, the European Directive EC/2001, and the principles enunciated in the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, October 2013).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS 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, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards

of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 07 March 2016. After a subsequent national phase, a licence was granted in the UK on 05 April 2016.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 5 mg desloratadine, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Tablet core:

Cellulose microcrystalline, partially pregelatinised maize starch, magnesium stearate and colloidal anhydrous silica

Tablet coating (Opadry blue):

Hypromellose 6cp, titanium dioxide (E171), microcrystalline cellulose, stearic acid and Indigo carmine (E132).

The finished product is packed into transparent polychlorotrifluoroethylene (PCTFE)/ polyvinyl chloride (PVC) or PVC/polyethylene (PE)/polyvinylidene chloride (PVDC) aluminium blister packs of 1, 2, 3, 5, 7, 10, 14, 15, 20, 21, 30, 50, 90 or 100 tablets. Not all pack sizes may be marketed.

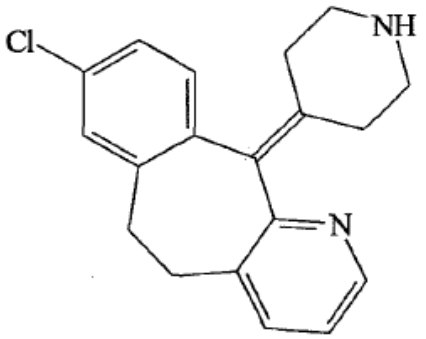
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Desloratadine

Chemical name: 8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Structure:



Molecular formula: $C_{19}H_{19}ClN_2$

Molecular weight: 310.8 g/mol

Description: White to off-white powder with pink cast.

Solubility; Very slightly soluble or practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in heptane.

Desloratadine was not the subject of a European Pharmacopoeia monograph at the time of assessment.

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

Synthesis of the active 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. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 5 mg desloratadine per tablet that are a generic version of the reference product Aerius 5 mg film-coated tablets. A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the tablet coat Opadry blue which is controlled to a suitable in-house specification. The indigo carmine (E132) constituent of the tablet coat is stated to comply with EU Directive 2008/128/EC (which supersedes 95/45/EC) on food additives used as colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the storage condition ‘Store in the original packaging.’

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

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Desloratadine tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of desloratadine is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of desloratadine.

Based on the data provided, Desloratadine tablets can be considered bioequivalent to Aerius 5 mg film-coated tablets (Merck Sharp & Dohme Ltd).

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence studies:

STUDY 1

The applicant submitted one bioequivalence study with their original submission. However, following recent regulatory action, the bioequivalence study that was performed to support this application was not considered suitable. The applicant therefore submitted two new bioequivalence studies to support this application.

The applicant submitted the following two bioequivalence studies:

STUDY 2
An open-label, randomised, single-dose, crossover, oral bioequivalence study of the applicant's test product Desloratadine 5 mg film coated tablets (Bristol Laboratories Ltd) versus the reference product Aerius 5 mg film-coated tablet (Merck Sharp & Dohme Ltd) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose (1 x 5 mg tablet) of the test or the reference product.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

Table: The mean pharmacokinetic (PK) results and 90% CI of the log-transformed PK parameters for desloratadine are presented in the table and graph below:

Bioequivalence Results:

TREATMENT A vs TREATMENT B

Parameter (N/N)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUC72 (pg.h/mL) (19 /19)	44723.49 48750.70 (43.11)	49870.81 54711.80 (43.73)	89.68	84.24 - 95.47	11.14
CMAX (pg/mL) (19 /19)	2631.21 2788.33 (33.78)	3123.46 3284.18 (30.72)	84.24	78.00 - 90.98	13.72
Tmax* (h) (19 /19)	5.00 (1.50 - 6.03)	3.00 (1.00 - 6.00)			

* Presented as median and range

TRT A=test product
TRT B=reference product
AUC_{0-72} area under the plasma concentration-time curve from zero to 72 hours
C_{max} maximum plasma concentration

Conclusion
Although the 90% C.I for AUC_{0-72} lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), this criteria was not met for C_{max}. Therefore the results failed to demonstrate that the test product desloratadine is bioequivalent to the reference product. This could probably be due to the number of drop-outs which was higher than expected, especially for desloratadine.

Based on the submitted bioequivalence study Desloratadine 5 mg film coated tablets (Bristol Laboratories Ltd) cannot be considered bioequivalent with Aerius 5 mg Tablets (Merck Sharp & Dohme Ltd.).

STUDY 3
An open-label, randomised, single-dose, crossover, oral bioequivalence study of the applicant's test product Desloratadine 5 mg film coated tablets (Bristol Laboratories Ltd) versus the reference product Aerius 5 mg film-coated tablet (Merck Sharp & Dohme Ltd) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose (1 x 5 mg tablet) of the test or the reference product.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

Table: The mean pharmacokinetic (PK) results and 90% CI of the log-transformed PK parameters for desloratadine are presented in the table and graph below:

Bioequivalence Results:

TREATMENT A vs TREATMENT B

Parameter (N/N)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUC72 (pg.h/mL) (30 /32)	58365.21 61370.94 (39.31)	57077.04 62989.34 (49.22)	102.26	97.03 - 107.77	12.03
CMAX (pg/mL) (32 /32)	3408.76 3612.44 (36.11)	3270.22 3538.68 (42.92)	104.24	98.45 - 110.36	13.53
Tmax* (h) (32 /32)	5.00 (1.00 - 6.50)	3.00 (1.00 - 7.00)			

* Presented as median and range

TRT A=test product
TRT B=reference product
AUC_{0-72} area under the plasma concentration-time curve from zero to 72 hours
C_{max} maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for desloratadine for the 5 mg test product strength lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product Desloratadine 5 mg film-coated tablets (Bristol Laboratories Ltd) is bioequivalent to the reference product Aerius 5 mg film-coated tablets (Merck Sharp & Dohme Ltd).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to desloratadine.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Hypersensitivity (including anaphylaxis, angioedema, dyspnea, pruritus, rash and urticaria) • Abnormal hepatic function (including hepatitis and elevated hepatic enzymes and bilirubin)
Important potential risks	• Seizure • Movement disorder (including psychomotor hyperactivity and restlessness) • Supraventricular tachyarrhythmiaHallucinations • Use in patients with severe renal insufficiency • Abnormal behaviour in paediatric patients (including anger, aggression and agitation) • Photosensitivity • QT prolongation
Missing information	• Effects on fertility • Use in pregnancy and lactation • Use in children below the age of 1 • Effects of desloratadine in poor metabolisers < 2 years of age

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's test product Desloratadine 5 mg film-coated tablets (Bristol Laboratories Ltd) and the reference product Aerius 5 mg film-coated tablets (Merck Sharp & Dohme Ltd).

The grant of a marketing authorisation is recommended for this application.

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 reference product Aerius 5 mg film-

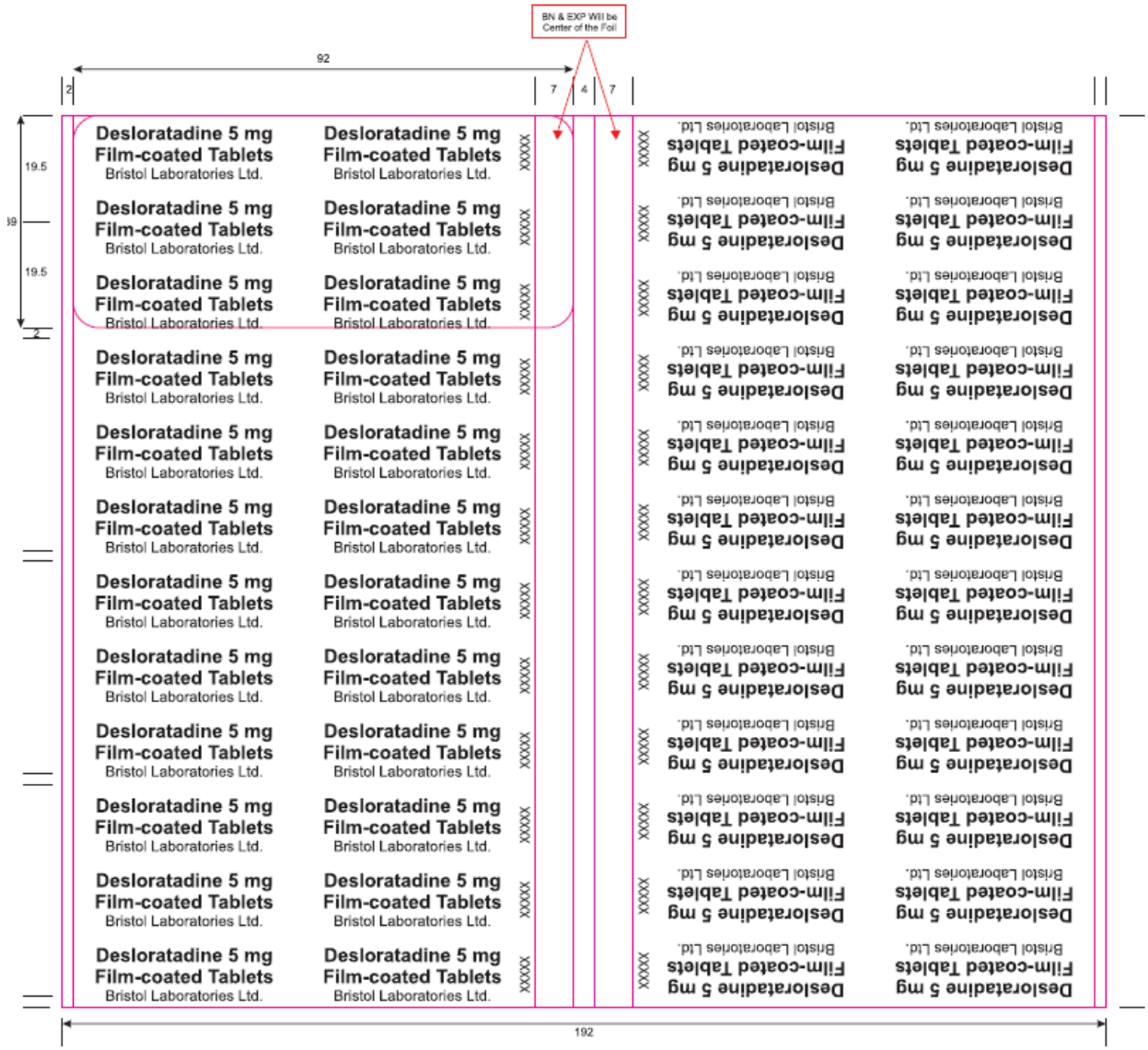
coated tablets (Merck Sharp & Dohme Ltd) for the content of the PIL and Ranitidine 300mg film-coated tablets (Bristol Laboratories Ltd; PL 17907/0030) for the style and layout of the PIL. The bridging report submitted by the applicant has been found acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation

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

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

The approved labelling for this medicine is presented below:


BN & EXP Will be Center of the Foil
92
2
7
4
7
19.5
19.5
2
Desloratadine 5 mg
Film-coated Tablets
Bristol Laboratories Ltd.
XXXXX
192