Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Azelastine hydrochloride 0.5 mg/ml Eye drops, solution

(Azelastine Hydrochloride)

UK Licence No: PL 25298/0145

Brown & Burk UK Limited

LAY SUMMARY

Azelastine hydrochloride 0.5 mg/ml Eye drops, solution

This is a summary of the Public Assessment Report (PAR) for Azelastine hydrochloride 0.5 mg/ml Eye drops, solution (PL 25298/0145). It explains how Azelastine hydrochloride 0.5 mg/ml Eye drops, solution was assessed, and its authorisation recommended, as well as its condition of use. It is not intended to provide practical advice on how to use Azelastine hydrochloride 0.5 mg/ml Eye drops, solution.

The product will be referred to as Azelastine hydrochloride Eye drops throughout the remainder of this public assessment report.

For practical information about using Azelastine hydrochloride Eye drops patients should read the package leaflet or contact their doctor or pharmacist.

What are Azelastine hydrochloride Eye drops and what are it used for?
Azelastine hydrochloride Eye drops are a 'hybrid generic medicine'. This means that Azelastine hydrochloride Eye drops are similar to a 'reference medicine' containing the same active substance already authorised in the UK called Optilast 0.5 mg/ml, Eye Drops, solution (PL 46302/0136; Mylan Products Limited).

Azelastine hydrochloride Eye drops is used in adults and children aged 4 years and above to treat and prevent eye disorders which the patient can get with hayfever (seasonal allergic conjunctivitis). Azelastine Eye drops can also be used for eye disorders caused by an allergy to substances such as house dust mites or animal hair (perennial allergic conjunctivitis) in adults and children aged 12 years and above.

How do Azelastine hydrochloride Eye drops work?
This medicine contains the active ingredient called azelastine hydrochloride, which belongs to a group of medicines called antiallergics (antihistamines). Antihistamines work by preventing the effects of substances such as histamine that the body produces as part of an allergic reaction. This medicine has been shown to reduce inflammation of the eye.

How are Azelastine hydrochloride Eye drops used?
This medicine is an eye drop solution for use in the eye(s) (ocular use).

The patient should always use this medicine exactly as their doctor or pharmacist has advised. If unsure, the patient should ask the doctor or pharmacist.

Azelastine hydrochloride Eye drops contain 0.125 mg benzalkonium chloride in each ml. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. The patient should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if the patient has dry eyes or disorders of the cornea (the clear layer at the front of the eye). If the patient feels an abnormal eye sensation, stinging or pain in the eye after using this medicine, they should talk to their doctor.

This medicine should only be applied to the eyes.

The recommended dose is:

Eye disorders caused by hayfever (seasonal allergic conjunctivitis)
• Use in adults and children aged 4 years and above.
• The usual dose is one drop in each eye in the morning and evening.
If the patient anticipates contact with pollen, the usual dose of Azelastine hydrochloride Eye drops may be taken as a preventive measure before going outside.

Eye disorders caused by an allergy (non-seasonal (perennial) allergic conjunctivitis)
• Use in adults and children aged 12 years and above
• The usual dose is one drop in each eye in the morning and evening.
If the patient's symptoms are severe, the doctor may increase the dose to one drop in each eye, up to four times a day.

Relief of symptoms of allergic conjunctivitis should be noticed after 15-30 minutes.

If possible, the patient should use Azelastine hydrochloride Eye drops regularly until their symptoms have disappeared.

Do not take Azelastine hydrochloride Eye drops for more than 6 weeks.

This medicine can only be obtained with a prescription.

For further information on how to use Azelastine hydrochloride Eye drops see section 3 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website

What benefits of Azelastine hydrochloride Eye drops have been shown in studies?
Since Azelastine hydrochloride Eye drops is a hybrid application, studies have been limited to tests to show that this medicine is pharmaceutically equivalent to the reference product Optilast 0.5 mg/ml, Eye Drops, solution (PL 46302/0136; Mylan Products Limited).On this basis, it is considered that Azelastine hydrochloride Eye drops is therapeutically equivalent to the reference product and its benefits and risks are taken to be the same. Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

What are the possible side effects from Azelastine hydrochloride Eye drops?
The most common side effects with Azelastine hydrochloride Eye drops (which may affect more than 1 in 10 people) are:

- Slight irritation (burning, itching, watering) in the eyes after putting Azelastine hydrochloride Eye drops. This should not last long.

For a full list of all the side effects reported with Azelastine hydrochloride Eye drops 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 was Azelastine hydrochloride Eye drops approved?
The MHRA decided that the benefits of Azelastine hydrochloride Eye drops are greater than the risks and recommended that it is approved for use.

What measures are being taken to ensure the safe and effective use of Azelastine hydrochloride Eye drops?

A Risk Management Plan has been developed to ensure that Azelastine hydrochloride Eye drops is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Azelastine hydrochloride Eye drops 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 Azelastine hydrochloride Eye drops

A Marketing Authorisation was granted in the UK on 13 September 2018.

The full PAR for Azelastine hydrochloride Eye drops follows this summary.

For more information about treatment with Azelastine hydrochloride Eye drops read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brown & Burk UK Limited a Marketing Authorisation for the medicinal product Azelastine hydrochloride Eye drops (PL 25298/0145) on 13 September 2018. The product is a prescription only medicine (POM), indicated for

- Seasonal allergic conjunctivitis
  The usual dosage in adults and children 4 years and older is one drop in each eye twice daily that can be increased, if necessary to four times daily. If allergen exposure is anticipated Azelastine hydrochloride Eye drops, solution should be administered prophylactically, prior to the exposure.

- Non-seasonal (perennial) allergic conjunctivitis
  The usual dosage in adults and children 12 years and older is one drop in each eye twice daily that can be increased, if necessary to four times daily.
  As safety and efficacy have been demonstrated in clinical trials for a period of up to 6 weeks, the duration of any course should be limited to a maximum of 6 weeks.
  Patients should be advised to contact their doctor if symptoms worsen or do not improve after 48 hours.

This application was submitted as abridged national application, according to Article 10(3) of directive 2001/83/EC, as amended, as a hybrid generic application. The reference medicinal product for this application is Optilast 0.5mg/ml Eye drops solution. Optilast 0.5mg/ml Eye drops solution was first authorised in the UK to Asta Medica Limited (PL 08336/0075-0076) via the mutual recognition procedure (UK/H/0255/001-002 and UK/H/0256/001-002) on 18 February 1998. Following subsequent change of ownership procedures, firstly to Valeant Pharmaceuticals Limited (PL 19166/0002) on 15 February 2002, then to Meda Pharmaceuticals Limited (PL 15142/0036) on 01 August 2009, the licence was authorised to the current Marketing Authorisation Holder; Mylan Products Limited (PL 46302/0136) on 12 April 2018.

The same MAH, Brown & Burk UK Limited, had a licence for the same product, Azelastine hydrochloride 0.5mg/ml Eye drops, solution (same composition and method of manufacture) granted in a decentralised procedure with the UK as RMS, PL 25298/0049; UK/H/3894/01/DC. This license was cancelled by the MAH, on 11 May 2015.

Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H1 antagonist properties. An additional anti-inflammatory effect could be detected after topical ocular administration. Data from in vivo (pre-clinical) and in vitro studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions e.g. leukotriene, histamine, PAF and serotonin.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being a hybrid medicinal product of the reference product that has been licenced for over 10 years.

Comparable physicochemical parameters between the reference medicinal product, a previously authorised Azelastine hydrochloride 0.5mg/ml Eye drops, solution (PL 25298/0049; UK/H/3894/01/DC) and proposed product were provided. As the product is a solution, no therapeutic equivalence study between the reference product Optilast 0.5 mg/ml, Eye Drops, solution (PL 46302/0136; Mylan Products Limited) the previously authorised Azelastine hydrochloride 0.5mg/ml Eye drops, solution (PL 25298/0049; UK/H/3894/01/DC) and the proposed product has been conducted.

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, assembly and batch release of these products.

For manufacturing sites within the Community, the MHRA 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.

A Marketing Authorisation was granted in the UK on 13 September 2018

II QUALITY ASPECTS

II.1 Introduction

Each drop of Azelastine hydrochloride Eye drops contain 0.015 mg azelastine hydrochloride (0.5 mg/ml). 1ml of Azelastine hydrochloride Eye drops also contains 0.125 mg of an excipient with known effect ; benzalkonium chloride. Other pharmaceutical excipients include hypromellose, disodium edetate, liquid sorbitol (crystallising), sodium hydroxide (for pH adjuster) and water for injections.

The finished product is packaged in 10 ml low density polyethylene (LDPE) Blow fill Seal (BFS) container with white polypropylene (PP) spiked cap having a tamper-proof base ring. One bottle contains either 6 ml, 8 ml or 10 ml solution. Not all pack sizes may be marketed.

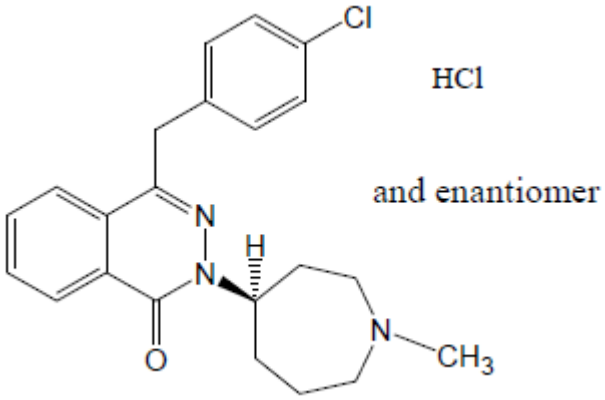
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Azelastine hydrochloride

Chemical name: (RS)-4-(4-chlorobenzyl)-2-(1-methylazepan-4-yl)phthalazin-1(2H)-one hydrochloride

Structure:



Molecular formula: $C_{22}H_{24}ClN_3O$, HCl

Molecular weight: 418.4 g/mol

Appearance: A white or almost white crystalline powder

Solubility: Sparingly soluble in water, soluble in ethanol and methylene chloride (according to Ph. Eur.)

The drug substance, azelastine hydrochloride is the subject of a European Pharmacopeia.

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a stable eye drop solution that could be considered as a hybrid medicinal product of the currently licensed product, Optilast 0.5 mg/ml, Eye Drops, solution (PL 46302/0136; Mylan Products Limited)

The physicochemical properties of the proposed product versus the reference product and previously authorised product; Azelastine hydrochloride 0.5mg/ml Eye drops, solution (PL 25298/0049;UK/H/3894/01/DC) have shown that the products are comparable.

All excipients comply with their respective European Pharmacopeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

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

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on production scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been 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 of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

The data from these studies support a shelf-life of 2 years for unopened bottles with no special storage conditions. The in-use shelf life of the product is 28 days after first opening the bottle.

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

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 azelastine hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview bases on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and 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 Azelastine hydrochloride Eye drops are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of azelastine hydrochloride are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In accordance with the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) "A waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved', therefore no bioequivalence study was conducted or required.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)
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 Azelastine hydrochloride Eye drops.

A summary of safety concerns, as approved in the RMP, are listed below:

Summary of safety concerns	
Important identified risk	Hypersensitivity
Important potential risks	Use in pregnancy, lactation and fertility
Missing information	Use in children under 4 years

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

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisation is recommended.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

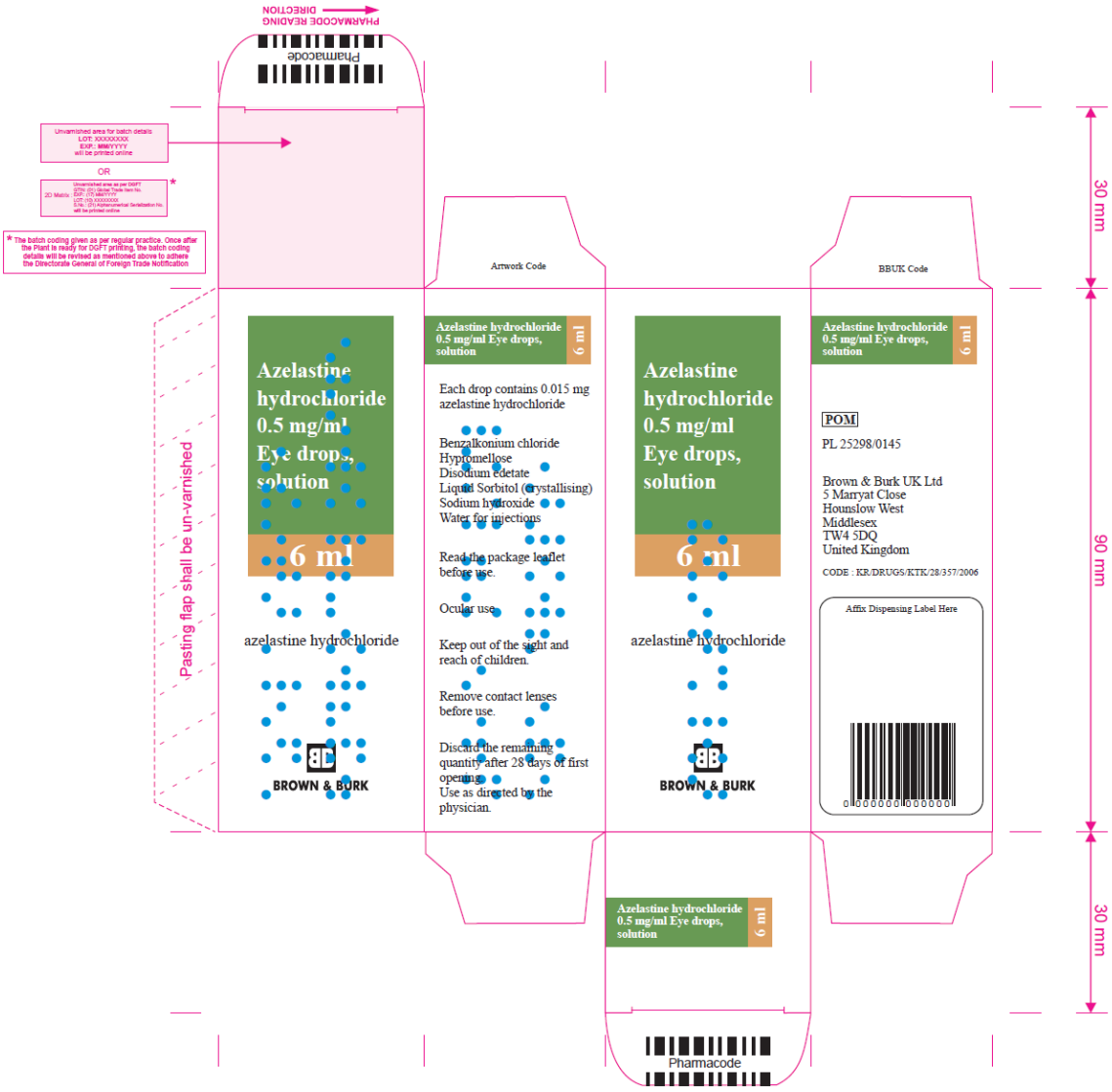
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The proposed product is identical to a previously authorised product, Azelastine hydrochloride 0.5mg/ml Eye drops, solution, and sufficient pharmaceutical data have been provided to show that these products are comparable to the reference product. . Extensive clinical experience with azelastine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

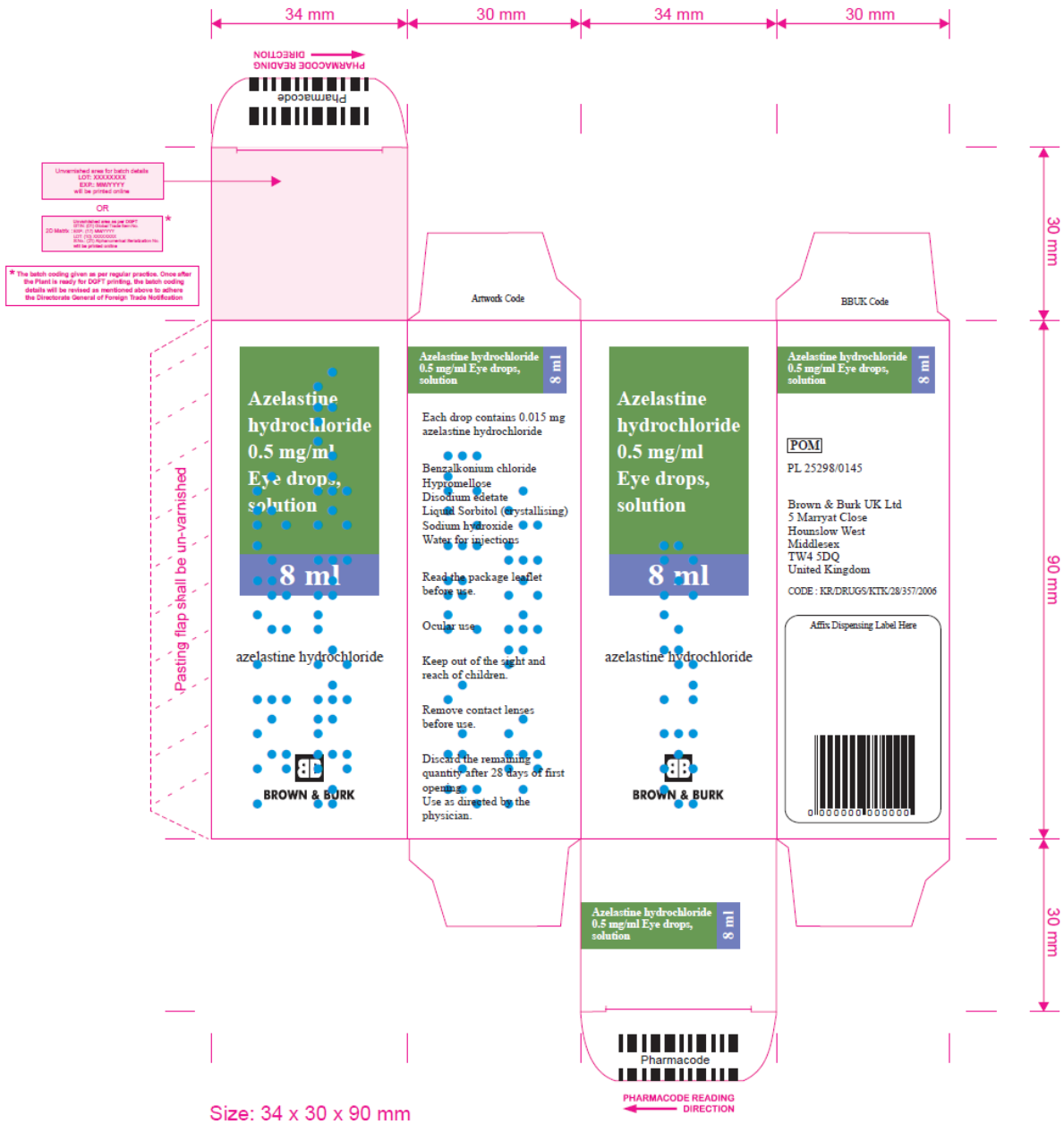
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

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 current approved labelling for this medicine is presented below:

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30 mm
34 mm
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30 mm
90 mm
30 mm
PHARMACODE READING DIRECTION
Pharmacode
Unvarnished area for batch details
LOT: XXXXXXXX
EXP.: MM/YYYY
will be printed online
OR
* The batch coding given as per regular practice. Once after the Plant is ready for DQFT printing, the batch coding details will be revised as mentioned above to adhere the Directorate General of Foreign Trade Notification
Pasting flap shall be un-varnished
Azelastine hydrochloride 0.5 mg/ml Eye drops, solution
8 ml
azelastine hydrochloride
BROWN & BURK
Artwork Code
Azelastine hydrochloride 0.5 mg/ml Eye drops, solution
8 ml
Each drop contains 0.015 mg azelastine hydrochloride
Benzalkonium chloride
Hypromellose
Disodium edetate
Liquid Sorbitol (Crystallising)
Sodium hydroxide
Water for injections
Read the package leaflet before use.
Ocular use.
Keep out of the sight and reach of children.
Remove contact lenses before use.
Discard the remaining quantity after 28 days of first opening.
Use as directed by the physician.
Azelastine hydrochloride 0.5 mg/ml Eye drops, solution
8 ml
azelastine hydrochloride
BROWN & BURK
Azelastine hydrochloride 0.5 mg/ml Eye drops, solution
8 ml
Pharmacode
PHARMACODE READING DIRECTION
BBUK Code
Azelastine hydrochloride 0.5 mg/ml Eye drops, solution
8 ml
POM
PL 25298/0145
Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom
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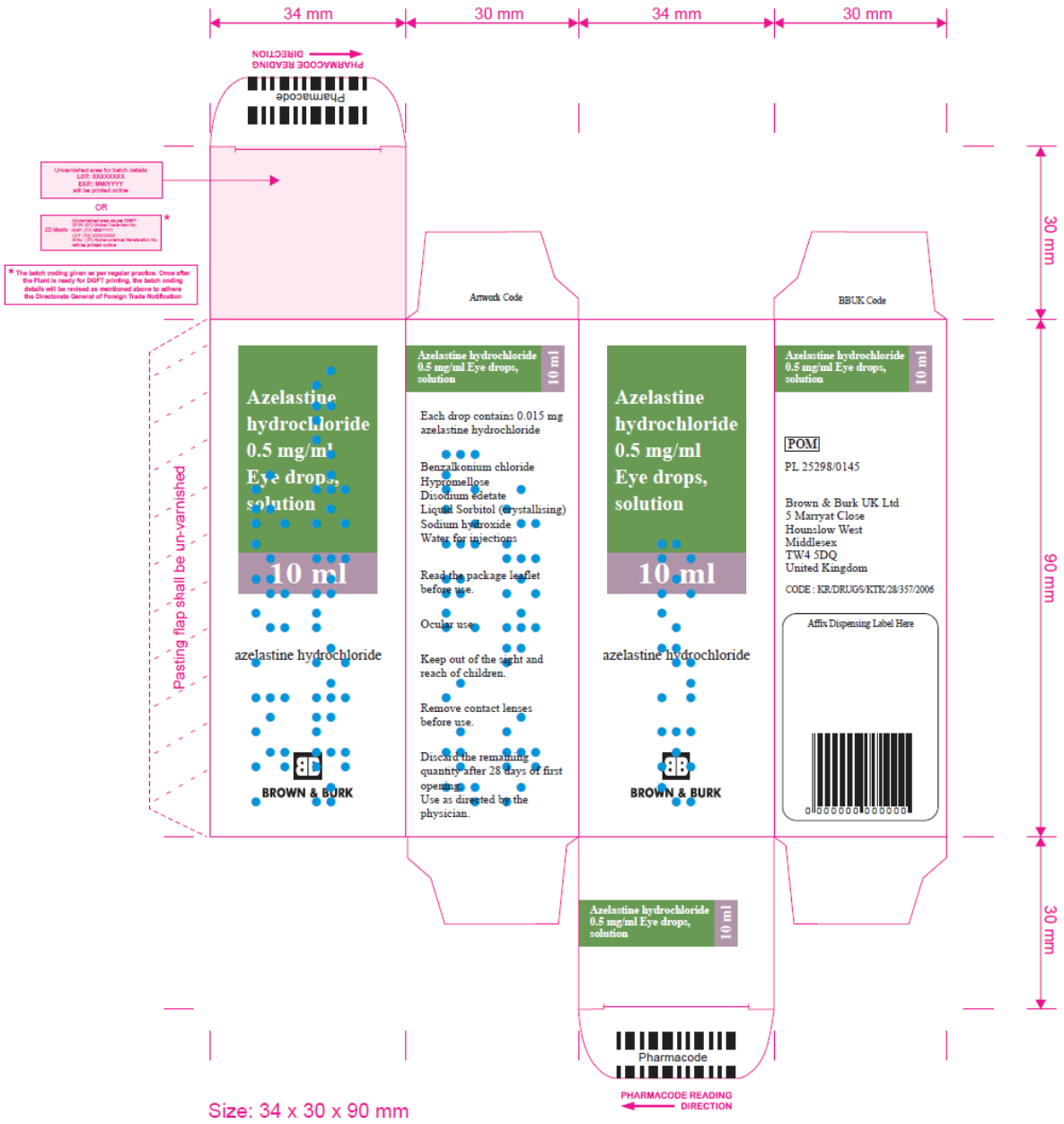

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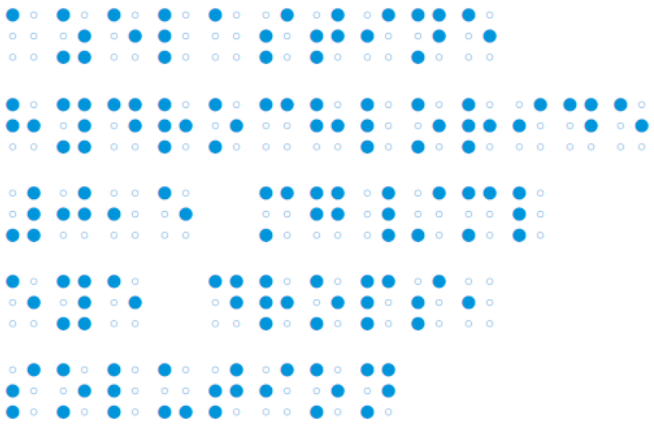

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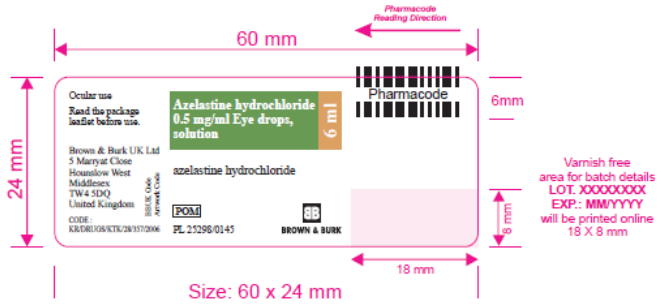

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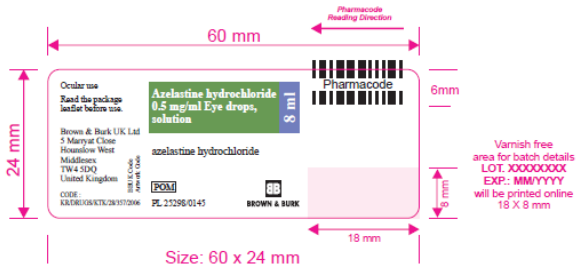

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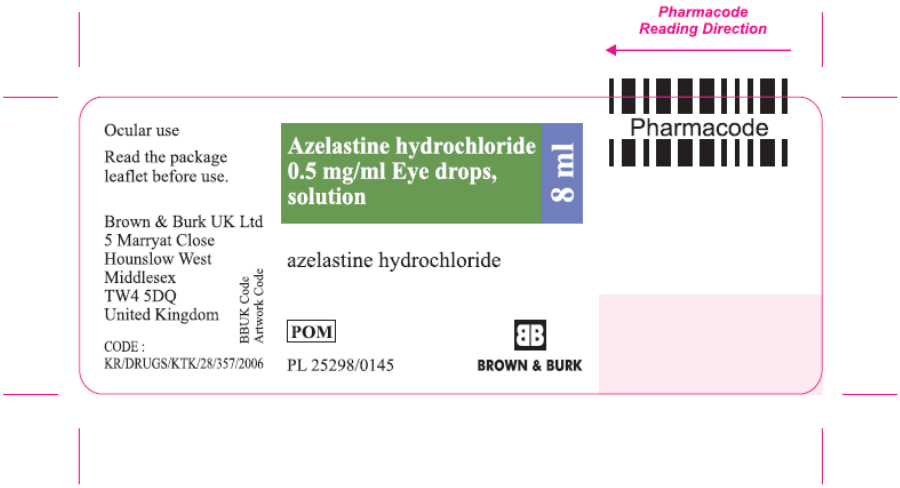

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18 X 8 mm

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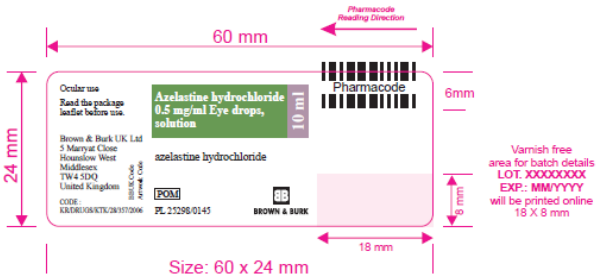

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Annex 1

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)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)