Public Assessment Report

UKPAR

CETIRIZINE DIHYDROCHLORIDE 10MG FILM-COATED TABLETS

BELL’S HEALTHCARE ALLERGY AND HAYFEVER RELIEF 10 MG TABLETS

(Cetirizine dihydrochloride)

UK Licence Numbers: PL 36390/0126-0127

Cipla (EU) Limited
LAY SUMMARY

Cetirizine Dihydrochloride 10mg Film-coated Tablets
Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets

(cetirizine dihydrochloride, film-coated tablets, 10 mg)

This is a summary of the Public Assessment Report (PAR) for Cetirizine Dihydrochloride 10mg Film-coated Tablets/Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets. It explains how Cetirizine Dihydrochloride 10mg Film-coated Tablets/Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets 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 Cetirizine Dihydrochloride 10mg Film-coated Tablets/Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets.

The products will collectively be referred to as Cetirizine Dihydrochloride 10mg Film-coated Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Cetirizine Dihydrochloride 10mg Film-coated Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Cetirizine Dihydrochloride 10mg Film-coated Tablets and what are they used for?
Cetirizine Dihydrochloride 10mg Film-coated Tablets are a ‘generic medicine’. This means that Cetirizine Dihydrochloride 10mg Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Zirtek Allergy/Zirtek Allergy Relief 10mg film-coated Tablets (UCB Pharma Limited; PL 00039/0542 and 0561).

Cetirizine Dihydrochloride 10mg Film-coated Tablets are indicated in adults and paediatric patients 6 years and above for the relief of:
• hayfever (allergic rhinitis) and year round allergies such as dust or pet allergies (perennial allergic rhinitis)
• chronic nettle rash (chronic idiopathic urticaria).
The patient must talk to their doctor if they do not feel better or if they feel worse after 3 days.

How do Cetirizine Dihydrochloride 10mg Film-coated Tablets work?
This medicine contains the active ingredient cetirizine dihydrochloride which belongs to a group of medicines called antihistamines. Cetirizine dihydrochloride blocks the effects of a substance called histamine which occurs naturally in the body. Histamine is involved in allergic reactions.

Antihistamines such as cetirizine dihydrochloride relieve the unpleasant symptoms and discomfort associated with these conditions such as sneezing, irritated, runny and blocked nose, itchy, red and watering eyes and skin rashes.

Cetirizine Dihydrochloride 10mg Film-coated Tablets can be obtained without prescription.

How are Cetirizine Dihydrochloride 10mg Film-coated Tablets used?
The pharmaceutical form of Cetirizine Dihydrochloride 10mg Film-coated Tablets is a film-coated tablet and the route of administration is oral (by mouth).

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

The **recommended dose of this medicine is:**

- **Adults and adolescents over 12 years of age:** One tablet (10mg) once daily. The patient’s doctor may prescribe them a starting dose of 5 mg (a half tablet) if this leads to satisfactory control of the symptoms.

- **Children aged from 6 to 12 years:** 5mg twice daily (a half tablet twice daily).

- **Children under 6 years:** Not recommended.

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

For further information on how Cetirizine Dihydrochloride 10mg Film-coated Tablets are used, please see the Summaries of Product Characteristics and package leaflets available on the MHRA website.

**What benefits of Cetirizine Dihydrochloride 10mg Film-coated Tablets have been shown in studies?**

Because Cetirizine Dihydrochloride 10mg Film-coated Tablets are a generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Zirtek Allergy/Zirtek Allergy Relief 10mg film-coated Tablets (UCB Pharma Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Cetirizine Dihydrochloride 10mg Film-coated Tablets?**

Because Cetirizine Dihydrochloride 10mg Film-coated Tablets are a generic medicine, the 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 Cetirizine Dihydrochloride 10mg Film-coated Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Cetirizine Dihydrochloride 10mg Film-coated Tablets approved?**

It was concluded that, in accordance with EU requirements, Cetirizine Dihydrochloride 10mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Zirtek Allergy/Zirtek Allergy Relief 10mg film-coated Tablets (UCB Pharma Limited). Therefore, the MHRA decided that, as for Zirtek Allergy/Zirtek Allergy Relief 10mg 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 Cetirizine Dihydrochloride 10mg Film-coated Tablets?
Safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Cetirizine Dihydrochloride 10mg Film-coated 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 Cetirizine Dihydrochloride 10mg Film-coated Tablets
The Marketing Authorisations for Cetirizine Dihydrochloride 10mg Film-coated Tablets (PL 33410/0043 and 0062) were granted in the UK to APSLA Limited on 09 June 2011.

A change of ownership was granted on 14 February 2013 to change the marketing authorisation holder to Cipla (EU) Limited (PL 36390/0126 and 0127).

The product name ‘Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets’ was approved for inclusion on PL licence number PL 36390/0127 on 11 March 2014

The full PAR for Cetirizine Dihydrochloride 10mg Film-coated Tablets follows this summary.

For more information about treatment with Cetirizine Dihydrochloride 10mg Film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2015.
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I  INTRODUCTION
The UK granted Marketing Authorisations for the medicinal product Cetirizine Dihydrochloride 10mg Film-coated Tablets (PL 33410/0043) and its duplicate licence (PL 33410/0062) to APSLA Limited on 9 June 2011.

Cetirizine Dihydrochloride 10mg Film-coated Tablets (PL 33410/0043) is available as a pharmacy only medicine under the supervision of a pharmacist. Cetirizine Dihydrochloride 10mg Film-coated Tablets (PL 33410/0062) is available as a GSL product and is sold without the supervision of a pharmacist in pack sizes of no greater than 30 tablets.

Cetirizine Dihydrochloride 10mg Film-Coated Tablets are for use in adults and children 6 years and above for the relief of nasal and ocular symptoms of perennial rhinitis and seasonal allergic rhinitis and the relief of symptoms of chronic idiopathic urticaria.

These are generic applications for Cetirizine Dihydrochloride 10mg Film-coated Tablets, submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applications refer to the UK reference (innovator) product, Zirtek 10mg, originally licensed to UCB S.A (PL 05221/0001) on 16 August 1988. The reference licence has since undergone two Change of Ownership (CoA) procedures; the first to UCB Waterford Limited on 23 March 2000 and subsequently to the current Marketing Authorisation Holder (MAH), UCB Pharma Limited UK (PL 00039/0542) on 12 December 2005. The second change of ownership resulted in separate licences being created for Pharmacy supply (PL 00039/0542) and GSL (Zirtek Allergy Relief/Zirtek Allergy 10mg Tablets (PL 00039/0561). The reference product has been authorised in the EEA for over 10 years.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Cetirizine Dihydrochloride is a well-established active substance that has had widespread clinical used for many years. These were applications for generic products, which will not be administered at a higher dosage, for a longer duration or for different indications that were previously authorised. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.

The pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

No new non-clinical or clinical studies were performed, which is acceptable given that the proposed product is a generic medicinal product of the reference product that has been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the MAH and it was, therefore, judged that the benefits of taking product Cetirizine
Dihydrochloride 10mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

The Marketing Authorisations for Cetirizine Dihydrochloride 10mg Film-coated Tablets (PL 33410/0043 and 0062) were granted in the UK to APSLA Limited on 09 June 2011. A change of ownership was granted on 14 February 2013 to change the marketing authorisation holder to Cipla (EU) Limited (PL 36390/0126 and 0127).

The product name ‘Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets’ was approved for inclusion on PL licence number PL 36390/0127 on 11 March 2014.
II.1 QUALITY ASPECTS

II.1 Introduction
Cetirizine Dihydrochloride 10mg Film-coated Tablets are presented as white coloured, circular, biconvex film-coated tablets, marked with ‘A’ on one side and a breakline score on the other. The tablets can be divided into equal halves. Each film-coated tablet contains 10 mg of cetirizine dihydrochloride. Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose (Avicel PH 102), lactose monohydrate for DC (Tabletose 80), colloidal anhydrous silica (Aerosil), maize starch, purified talc, magnesium stearate making up the tablet core; Opadry White which makes up the film coating consists of hypromellose 15cP, lactose monohydrate, titanium dioxide, macrogol and sodium citrate which are controlled by an in-house specification and is satisfactory.

The finished product is presented in blisters composed of aluminium and clear polyvinyl chloride (PVC) which are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of either:
- 7, 14, 21, 28, 30 or 60 tablets for PL 36390/0126
- 4, 5, 7, 14 or 30 tablets for PL 36390/0127

The MA Holder (MAH) has stated that not all pack sizes may be marketed however, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

II.2 DRUG SUBSTANCE
Cetirizine dihydrochloride
INN: Cetirizine dihydrochloride
Chemical name: (RS)-2-[2-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride.

Structure:

\[
\text{\begin{tikzpicture}
  \draw[thick] (-1,0) -- (1,0);
  \draw[thick] (0,-1) -- (0,1);
  \filldraw[black] (-1,0) circle (0.05 cm);
  \filldraw[black] (1,0) circle (0.05 cm);
  \filldraw[black] (0,-1) circle (0.05 cm);
  \filldraw[black] (0,1) circle (0.05 cm);
  \draw[thick] (-1,0) -- (-1,-1);
  \draw[thick] (1,0) -- (1,-1);
  \draw[thick] (0,-1) -- (0,-2);
  \draw[thick] (0,1) -- (0,2);
  \draw[thick] (-1,-1) -- (-1,-2);
  \draw[thick] (1,-1) -- (1,-2);
  \draw[thick] (-1,0) -- (-1,2);
  \draw[thick] (1,0) -- (1,2);
  \draw[thick] (0,-1) -- (0,2);
  \draw[thick] (-1,0) -- (1,0);
  \draw[thick] (0,-1) -- (0,1);
  \draw[thick] (-1,0) -- (0,-1);
  \draw[thick] (1,0) -- (0,1);
  \draw[thick] (0,-1) -- (-1,0);
  \draw[thick] (0,1) -- (1,0);
  \node at (-1.25,0) {HCl};
  \node at (1.25,0) {HCl};
  \node at (0,-1.25) {HCl};
  \node at (0,1.25) {HCl};
\end{tikzpicture}}
\]

Molecular formula: C\textsubscript{21}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{3}.2(HCl)
Molecular mass: 461.81

General Properties
Description: A white or almost white powder, freely soluble in water, and practically insoluble in acetone and in methylene chloride.
Cetirizine dihydrochloride is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product
Pharmaceutical Development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop robust, stable, generic formulation, bioequivalent to the innovator product Zirtek Allergy 10 mg Tablets first licensed in the UK on 16 August 1988 to UCB SA.

Comparative impurity and dissolution profiles were provided for the test and reference products and were found to be similar.

Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their relevant European Pharmacopoeia (Ph. Eur) monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate none of the excipients used contain material derived from animal or human consumption. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

Manufacturing Process
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

Finished Product Specification
Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a
shelf-life of 3 years has been set which is satisfactory. This medicinal product does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

**Bioequivalence Study**

A bioequivalence study was presented under fasting conditions comparing the test product, Cetirizine 10mg Tablets to the reference product; Zirtek Allergy 10mg Tablets, UCB, UK (PL 00039/0542).

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**

**III.1 introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of cetirizine dihydrochloride are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology 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 Cetirizine Dihydrochloride 10mg Film-coated 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 applications were based on being generic medicinal products of an originator product that has been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.
IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of cetirizine dihydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 cetirizine dihydrochloride.

IV.2 Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study. The reference product used for the bioequivalence study is Zirtek Allergy 10 mg Tablets (PL 00039/0542), UCB Pharma Limited UK.

This is a single dose, randomised, balanced, two-way crossover comparative oral bioavailability study of Cetirizine Dihydrochloride 10mg Film-coated Tablets (test product) and Zirtek Allergy 10 mg Tablets (UCB Pharma Limited, UK) in healthy adults under fasting conditions.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

Study design
A single dose of the investigational products (1 tablet of 10mg) was administered orally to each subject in each period with 240 ml of water after an overnight fast of at least 10 hours.

Serial blood sampling before dosing and up to 48 hours after drug administration was carried out.

A washout period of 7 days was maintained between the two dosing periods in each group which is sufficient time for cetirizine dihydrochloride to be eliminated from the body.

A validated HPLC-MS/MS analytical methodology was used for quantification of Cetirizine dihydrochloride from the human plasma samples. Primary variables analysed were: $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, and additional pharmacokinetic parameters were $t_{\text{max}}$, $t_{1/2}$, $\text{MRT}$ and $\text{AUC}\%\text{ Extrap}$.

Results
All volunteers completed both treatment periods and their data were included in the statistical analysis.
There were no protocol deviations.
Baseline plasma levels were zero at period 2, indicating that the washout period was adequate.
The results are summarised in Tables 1 and 2.
Table 1. Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geom. Mean</th>
<th>Arith. Mean</th>
<th>Std. Dev.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Ref</td>
<td>Test</td>
<td>Ref</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>327.01</td>
<td>320.54</td>
<td>43.16</td>
<td>54.08</td>
</tr>
<tr>
<td></td>
<td>417.47</td>
<td>477.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/ml)</td>
<td>2565.73</td>
<td>2591.52</td>
<td>439.09</td>
<td>435.85</td>
</tr>
<tr>
<td></td>
<td>3870.1</td>
<td>3572.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-infty} (ng.h/ml)</td>
<td>2591.52</td>
<td>2617.57</td>
<td>447.67</td>
<td>445.60</td>
</tr>
<tr>
<td></td>
<td>3917.7</td>
<td>3618.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.78</td>
<td>9.58</td>
<td>1.15</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>12.17</td>
<td>12.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>7.77</td>
<td>7.24</td>
<td>1.03</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>10.39</td>
<td>9.72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

Table 2: Summary of pharmacokinetic data for Cetirizine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric Mean</th>
<th>Point estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>327.01</td>
<td>320.54</td>
<td>101.26%</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/ml)</td>
<td>2565.73</td>
<td>2591.52</td>
<td>98.57%</td>
</tr>
<tr>
<td>AUC_{0-infty} (ng.h/ml)</td>
<td>2591.52</td>
<td>2617.57</td>
<td>98.76%</td>
</tr>
</tbody>
</table>

Conclusion
The 90% Confidence Intervals for the geometric ratios from In-transformed data of C_{max}, AUC_{0-t}, and AUC_{0-infty} of Cetirizine dihydrochloride, were within the bioequivalence acceptance range (80-125%). Based on these results, Cetirizine Dihydrochloride 10mg Film-coated Tablets (Test) is bioequivalent with that of Zirtek Allergy 10 mg Tablets (Reference) of UCB Pharma Limited, UK, under fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been provided and none are required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data have been submitted and none is required for these applications.

IV.5 Clinical safety
A total of 6 non-serious adverse events were reported during the study (3 related to the test formulation and 3 related to the reference formulation). No serious or severe adverse event was reported during the study and both formulations were well tolerated. No new safety data have been submitted and none are required for this application.
IV.5  Clinical safety
No new safety data have been provided and none are required for an application of this type.

IV.6  Discussion on the clinical aspects
SmPC, PIL, Labels
The SmPCs, PILs and labels are medically acceptable. The SmPCs are consistent with that for the originator product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
There are no objections to approval of Cetirizine Dihydrochloride 10mg Film-coated Tablets from a clinical point of view.

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 package leaflet 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.
VI Overall conclusion, benefit/risk assessment and recommendation

QUALITY
The important quality characteristics of Cetirizine Dihydrochloride 10mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
The applicant’s Cetirizine Dihydrochloride 10mg Film-coated Tablets has been demonstrated to be generic version of the reference product, Zirtek Allergy 10 mg Tablets, currently authorised to UCB Pharma Limited UK (PL 00039/0542) on 12 December 2005 and originally granted to UCB SA on 16 August 1988.

No new or unexpected safety concerns arise from these applications.

RISK-Benefit ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Cetirizine Dihydrochloride 10mg Film-coated Tablets and the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma Limited, UK) are interchangeable. Extensive clinical experience with cetirizine dihydrochloride is considered to have demonstrated the therapeutic value of the active substances. The risk benefit is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The Summary of Product Characteristics and Patient Information Leaflet (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 Cetirizine Dihydrochloride 10mg Film-coated Tablets is presented below:
CETIRIZINE DIHYDROCHLORIDE 10MG FILM-COATED TABLETS
PL 36390/0126 and 0127

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following table lists non-urgent safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/03/2014</td>
<td>Change of ownership</td>
<td>Change of ownership from PL 33410/0043 &amp; 0062 (APSLA Limited) to PL 36390/0126 and 0127 (Cipla (EU) Limited).</td>
<td>Approved on 09/04/2014.</td>
</tr>
<tr>
<td>19/12/2013</td>
<td>Type 1B</td>
<td>PL 36390/0127-0011: To add ‘Bell Sons Co Druggist Limited’ as an Own Label Supplier and to add the product name, ‘Bell’s Healthcare Allergy and Hayfever Relief 10 mg Tablets’ to the licence. As a consequence section 1 of the SmPC and the PIL and Label have been updated. The label and leaflet mock ups for Bell’s Healthcare have been approved.</td>
<td>Approved on 11/03/2014</td>
</tr>
<tr>
<td>10/03/2014</td>
<td>Type 1B</td>
<td>PL 36390/0127-0015: To add the pack size of 30 tablets. As a consequence, section 6.5 (container) of the SmPC, the PIL and label have been updated.</td>
<td>Approved on 09/04/2014</td>
</tr>
<tr>
<td>17/08/2015</td>
<td>Type II</td>
<td>PL 36390/0126-0020 and PL 36390/0127-0024: To submit additional/replacement bioequivalence study.</td>
<td>Approved on 19/10/2015- see Annex 1</td>
</tr>
</tbody>
</table>
Our Reference: PL 36390/0126-0020  
PL 36390/0127-0024

Product: Cetirizine Dihydrochloride 10mg Film-coated Tablets  
Bell's Healthcare Allergy and Hayfever Relief 10 mg Tablets

Marketing Authorisation Holder: Cipla (EU) Limited
Active Ingredient(s): Cetirizine dihydrochloride

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To submit additional/replacement bioequivalence study.

Supporting Evidence
The applicant has submitted a new bioequivalence study to replace the old study. It uses the same reference product Zirtek Allergy Relief 10 mg film-coated tablets.

Evaluation
The following bioequivalence study was submitted in support of this variation:

An open label, randomised, single dose, two-treatment, two period, two sequence crossover study to compare the pharmacokinetics of the test product Cetirizine Dihydrochloride 10mg Film-coated Tablets (Cipla (EU) Limited) versus the reference product, Zirtek Allergy Relief 10 mg film coated tablet (UCB Pharma Ltd; UK), in healthy subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (10 mg) of either the test or the reference product as per the randomisation schedule. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:
Table 1: Pharmacokinetic data for cetirizine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Test product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-∞ (hr. ng /ml)</td>
<td>3585.70 (±871.96)</td>
<td>3345.70 (±707.97)</td>
</tr>
<tr>
<td>AUC₀-t (hr. ng /ml)</td>
<td>3734.31 (±1030.41)</td>
<td>3492.79 (±840.27)</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>435.78 (±101.99)</td>
<td>396.62 (±74.41)</td>
</tr>
<tr>
<td>tₘₐₓ (hr)</td>
<td>0.67 (0.50 – 2.00)</td>
<td>0.67 (0.33 – 2.00)</td>
</tr>
</tbody>
</table>

1 Median (Min, Max)

AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
AUC₀-t area under the plasma concentration-time curve from zero to t hours
Cₘₐₓ maximum plasma concentration
Tₘₐₓ Time to reach Cₘₐₓ

Table 2: Bioequivalence evaluation of cetirizine

<table>
<thead>
<tr>
<th>Pharmacokinetic</th>
<th>Geometric Mean Ratio Test/Ref (%)</th>
<th>Confidence Intervals</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (0-t)(hr ng/mL)</td>
<td>106.61</td>
<td>102.38 - 111.01</td>
<td>7.98</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>108.84</td>
<td>102.23 - 115.88</td>
<td>12.39</td>
</tr>
</tbody>
</table>

**Bioequivalence study conclusion**
The bioequivalence study conducted is acceptable. It was well designed and executed, with appropriate sampling schedules and washout. The statistical analyses, measures used and the bioequivalence limits set were all as per the current bioequivalence guidance. The individual raw data and concentration time curves are acceptable. The bioanalysis plan and reanalysis schedule are all acceptable.

The 90% confidence intervals of the test/reference ratio for AUC, and Cₘₐₓ values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the test product Cetirizine Dihydrochloride 10mg Film-coated Tablets (Cipla (EU) Limited) is bioequivalent to the reference product Zirtek Allergy Relief 10 mg film coated tablet (UCB Pharma Ltd; UK).

Bioequivalence has been shown with this new study.

**Conclusion**
The bioequivalence study submitted is acceptable.

**Decision** - Approved on 16 October 2015.