Public Assessment Report

Decentralised Procedure

Benadryl Allergy Liquid Release 10 mg Capsules
(cetirizine dihydrochloride)

Procedure No: UK/H/3765/001/DC

UK Licence No: PL 15513/0378

McNeil Products Limited
LAY SUMMARY

On 27 February 2011, Estonia, Greece, France, Ireland, Italy, Latvia, Portugal, Slovenia and the UK agreed to grant a Marketing Authorisation to Catalent Pharma Solutions Limited for the medicinal product Benadryl Allergy Liquid Release 10 mg Capsules (PL 31859/0002; UK/H/3765/01/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 20 April 2011. The licence then underwent a change of ownership to McNeil Products Limited (PL 15513/0378), which was approved on 16 June 2011.

Benadryl Allergy Liquid Release 10 mg Capsules is a General Sales List (GSL) medicine used to relieve the symptoms of hay fever and other allergic conditions, such as pet or dust allergies. This medicine can also be used to treat allergic skin reactions. These include urticaria, also known as hives, where the skin looks blotchy, with white raised wheals (bumps) surrounded by redness. Benadryl Allergy Liquid Release 10 mg Capsules are for use in adults and children aged 12 years and over.

Benadryl Allergy Liquid Release 10 mg Capsules contain the active ingredient cetirizine dihydrochloride, which is an antihistamine that helps relieve allergy symptoms such as sneezing, runny nose and watery eyes.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Benadryl Allergy Liquid Release 10 mg Capsules outweigh the risks; hence a Marketing Authorisation was granted.
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## Module 1
### Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Names</strong></th>
<th>Benadryl Allergy Liquid Release 10 mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Cetirizine dihydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Capsule, soft</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Catalent Pharma Solutions Ltd.</td>
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<tr>
<td></td>
<td>Frankland Road</td>
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<td></td>
<td>Blagrove</td>
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<td>Swindon</td>
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<td></td>
<td>Wiltshire SN5 8RU</td>
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<td></td>
<td>United Kingdom</td>
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<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Estonia, Greece, France, Ireland, Italy, Latvia, Portugal and Slovenia</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3765/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 27 February 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Carton:
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMS) considered that the application for Benadryl Allergy Liquid Release 10 mg Capsules (PL 31859/0002; UK/H/3765/001/DC) could be approved.

The product is a General Sales Licence (GSL) medicine indicated in adults and paediatric patients 12 years and above for the relief of:

- nasal and ocular symptoms of seasonal and perennial allergic rhinitis
- symptoms of chronic idiopathic urticaria.

The application was submitted using the Decentralised Procedure (DCP), with the UK as RMS and Estonia, Greece, France, Ireland, Italy, Latvia, Portugal and Slovenia as CMS. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Zirtek Allergy 10 mg Tablets (UCB Pharma, UK), which was first authorised in the UK on 16 August 1988.

Benadryl Allergy Liquid Release 10 mg Capsules contain the active ingredient cetirizine dihydrochloride. Cetirizine dihydrochloride is a selective histamine H1 receptor antagonist, which inhibits the histamine-mediated "early" phase of the allergic reaction and reduces the migration of inflammatory cells/release of inflammatory mediators associated with the "late" allergic response.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

One single-dose, bioequivalence study was submitted to support this application, comparing the test product Benadryl Allergy Liquid Release 10 mg Capsules (Catalent Pharma Solutions Limited, UK) with the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of this bioequivalence study, no new clinical studies were performed, 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.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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, 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 (Day 210) on 27 February 2011. After a subsequent national phase, a licence was granted in the UK on 20 April 2011. The licence then underwent a change of ownership to McNeil Products Limited (PL 15513/0378), which was approved on 16 June 2011.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Benadryl Allergy Liquid Release 10 mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cetirizine dihydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Piperazine derivatives, (ATC code: R06A E07)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Capsule, soft 10mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3765/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Estonia, Greece, France, Ireland, Italy, Latvia, Portugal and Slovenia</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 31859/0002</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Catalent Pharma Solutions Ltd.</td>
</tr>
<tr>
<td></td>
<td>Frankland Road</td>
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<td>Blagrove</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Cetirizine dihydrochloride

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

Structure:

![Chemical Structure](image)

Molecular formula: C_{21}H_{25}ClN_{2}O_{3}\cdot2\text{HCl}

Molecular Mass: 461.8

Appearance: 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.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the capsule, the capsule shell and the printing ink namely, Macrogol 600, potassium hydroxide 43% w/w, povidone K30, purified water, gelatin, sorbitol (E420), glycerol, lecithin, medium chain triglycerides, propylene glycol, black iron oxide (E172), polyvinyl acetate phthalate, Macrogol 400 and ammonium hydroxide. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of potassium hydroxide 43% w/w, lecithin, polyvinyl acetate phthalate and black iron oxide (E172). Potassium hydroxide 43%w/w and black iron oxide (E172) are controlled to suitable in-house specifications. Lecithin and polyvinyl acetate phthalate are controlled to suitable US Pharmacopoeia monograph-National Formulary specifications. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. A Certificate of Suitability from the European Directorate for the Quality of Medicines (EDQM) has been provided for the supplier of gelatin, showing compliance with current guidelines concerning the minimising of TSE/BSE transmission.

No genetically modified organisms (GMO) have been used in the preparation of the excipients.
Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product that contained 10 mg cetirizine dihydrochloride and could be considered a generic medicinal product of the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product versus the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. No process validation data have been generated. However, in-line with the Notes for Guidance on Process Validation (CPMP/QWP/848/96), the Marketing Authorisation Holder has provided a commitment to submit data for validation performed on maximum full-scale batches as soon as it is available.

Control of Finished Product
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The capsules are packaged in colourless polvinylchloride/polyethylene/polvinylidene chloride (PVC/PE/PVDC) blisters sealed with aluminium lidding foil. The blisters are packed in cartons of 7 capsules.

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 foodstuff.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with the storage conditions “Store below 30°C.”

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

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive
2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
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 overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The clinical pharmacology of cetirizine dihydrochloride is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-way, crossover study comparing the pharmacokinetics of the test product Benadryl Allergy Liquid Release 10 mg Capsules (Catalent Pharma Solutions Limited, UK) and the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK) in healthy male subjects under fasting conditions.

The subjects were administered 10 mg of test or reference product with 240ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was at least 5 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (arithmetic mean ± standard deviation, ratio and confidence intervals [CI]) of cetirizine dihydrochloride

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Benadryl Allergy 10 mg (Test)</th>
<th>Zirtek Allergy 10 mg (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t (ng.h/ml)</td>
<td>3407.974±330.429</td>
<td>3450.991±383.048</td>
<td>0.99</td>
<td>0.97-1.01</td>
</tr>
<tr>
<td>AUC₀-inf (ng.h/ml)</td>
<td>3532.311±384.132</td>
<td>3604.230±417.455</td>
<td>0.98</td>
<td>0.96-1.00</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>339.881±46.911</td>
<td>326.729±58.269</td>
<td>1.05</td>
<td>1.00-1.09</td>
</tr>
</tbody>
</table>

AUC₀-∞: area under the plasma concentration-time curve from time zero to infinity
AUC₀-t: area under the plasma concentration-time curve from time zero to t hours
C_max: maximum plasma concentration
Ratio and 90% CI calculated from ln-transformed data

The current Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for C_max and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC₀-t, AUC₀-inf and C_max lie within the acceptable limits. Thus, the data support the claim that the test product Benadryl Allergy Liquid Release 10 mg Capsules (Catalent Pharma Solutions Limited, UK) is bioequivalent to the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK).

EFFICACY

The efficacy of cetirizine dihydrochloride is well-known. No new efficacy data have been submitted and none are required for an application of this type.

SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised by the bioequivalence data.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL),
Labels
The SmPC, PIL and labels are clinically acceptable. The SmPC is consistent with that for the
originator product. The PIL is consistent with the details in the SmPC and in-line with the
current guidelines. The labelling is in-line with the current guidelines.

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

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and
provides adequate evidence that the applicant 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.

Suitable justification has been provided for not submitting a Risk Management Plan for this
product.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV  OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Benadryl Allergy Liquid Release 10 mg Capsules 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 this type of application.

Efficacy
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Benadryl Allergy Liquid Release 10 mg Capsules and the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK).

SAFETY
The safety profile of cetirizine dihydrochloride is well-known. No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference product, where appropriate, along with with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the reference product Zirtek Allergy 10 mg Tablets (UCB Pharma, UK). Extensive clinical experience with cetirizine dihydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>16/05/2013</td>
<td>IB</td>
<td>To fulfil the post-approval commitment made during the repeat-use MRP procedure by submitting the Environmental Risk Assessment Report and the curriculum vitae of the relevant expert.</td>
<td>Granted: 03/07/2013</td>
</tr>
</tbody>
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Annex 1

Reference: PL 15513/0378-0012
Product: Benadryl Allergy Liquid Release 10 mg Capsules
Marketing Authorisation Holder: McNeil Products Limited (Change of ownership from Catalent Catalent Pharma Solutions Limited, approved on 16 June 2011)
Active Ingredient(s): Cetirizine dihydrochloride

Reason
To fulfil the post-approval commitment made during the repeat-use MRP procedure, involving Bulgaria, Germany, Lithuania and Romania, by submitting the Environmental Risk Assessment Report and the curriculum vitae of the relevant expert.

Supporting evidence
An Environmental Risk Assessment Report for Benadryl Allergy Liquid Release 10 mg Capsules and the curriculum vitae of the Environmental Risk Assessor have been provided.

Evaluation
The applicant has provided an acceptable environmental risk assessment (ERA), in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP4447/00). The report was produced by a suitably qualified and experienced expert.

Conclusion
The Environmental Risk Assessment is acceptable.

Decision: Approved on 3 July 2013.