Public Assessment Report

Acrivastine 8mg Capsules, hard
Brown & Burk Allergy Relief 8mg capsules, hard
(acrivastine)

UK Licence Number/s: PL 48468/0001-0002

Vivalabs Europe Limited
Lay Summary
Acrivastine 8mg Capsules, hard
Brown & Burk Allergy Relief 8mg capsules, hard

(acrivastine)

This is a summary of the Public Assessment Report (PAR) for Acrivastine 8mg Capsules, hard (PL 48468/0001) and Brown & Burk Allergy Relief 8mg capsules, hard (PL 48468/0002). It explains how Acrivastine 8mg Capsules, hard and Brown & Burk Allergy Relief 8mg capsules, hard 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 Acrivastine 8mg Capsules, hard and Brown & Burk Allergy Relief 8mg capsules, hard.

The products will be referred to as ‘Acrivastine Capsules’ throughout the remainder of this public assessment report (PAR).

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

What are Acrivastine Capsules and what are they used for?
Acrivastine Capsules are a ‘generic medicine’. This means that Acrivastine Capsules are similar to a ‘reference medicines’ already authorised in the European Union (EU) called Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited).

Acrivastine Capsules are used in adults under 65 years old and adolescents aged 12 years and over to relieve the symptoms of hay fever and other allergic conditions such as pet or dust allergies. Acrivastine Capsules can also be used to treat the symptoms of urticaria, also known as hives, where the skin looks blotchy with white raised wheals (bumps) surrounded by redness.

How do Acrivastine Capsules work?
The active ingredient in Acrivastine Capsules is acrivastine, which is an antihistamine that helps relieve allergy symptoms such as sneezing, runny nose and watery eyes.

How are Acrivastine Capsules used?
The pharmaceutical form of Acrivastine Capsules is a hard capsule and the route of administration is oral (by mouth).

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

The patient should take their medicine in accordance with the information in the following table.

The patient should not take more than the stated dose shown in table.

Children under 12 years old
This medicine is not recommended for children aged under 12 years.

Adults and Adolescents 12 – 65 years old

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents 12-65 years</td>
<td>1 Capsule up to 3 times a day.</td>
</tr>
<tr>
<td>• Do not take more than 3 doses in 24 hours.</td>
<td></td>
</tr>
<tr>
<td>• If symptoms persist talk to your doctor.</td>
<td></td>
</tr>
</tbody>
</table>

Adults over 65 years
This medicine is not recommended for adults aged over 65 years old.
For further information on how Acrivastine Capsules are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

**What benefits of Acrivastine Capsules have been shown in studies?**
Because Acrivastine Capsules are ‘generic medicines’, studies in patients have been limited to tests to determine that Acrivastine Capsules are bioequivalent to the reference product, Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products 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 Acrivastine Capsules?**
Because Acrivastine Capsules are generic medicines that are considered bioequivalent to the reference medicine; Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited), the possible side effects are taken as being the same as those of the reference medicine.

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

**Why were Acrivastine Capsules approved?**
It was concluded that, in accordance with EU requirements, Acrivastine Capsules have been shown to have comparable quality and to be bioequivalent to Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited) and the benefits are greater than its risks Therefore, the MHRA decided that, as for Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited); 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 Acrivastine Capsules?**
A risk management plan (RMP) has been developed to ensure that Acrivastine Capsules 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 Acrivastine Capsules 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 Acrivastine Capsules**
The UK agreed to grant Marketing Authorisations for Acrivastine Capsules on 26 November 2018.

The full PAR for Acrivastine Capsules follows this summary.

This summary was last updated in January 2019.
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I. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Vivalabs Europe Limited Marketing Authorisations for the medicinal products; Acrivastine 8mg Capsules, hard (PL 48468/0001) and Brown & Burk Allergy Relief 8mg capsules, hard (PL 48468/0002). Acrivastine 8mg Capsules, hard (PL 48468/0001) are available via pharmacies (P) and Brown & Burk Allergy Relief 8mg capsules, hard (PL 48468/0002) are available on the general sales list (GSL). These medicines are indicated for symptomatic relief of allergic rhinitis, including hay fever, and to treat the symptoms of chronic idiopathic urticaria.

The applications for Acrivastine Capsules were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Benadryl Allergy Relief (PL 15513/0035) and Benadryl Allergy Relief (PL 15513/0128) authorised to the Marketing Authorisation Holder; McNeil Products Limited on 17 September 1997 and 08 March 2005 respectively. The two applications are for the same product with identical indications, differing only in legal status (P and GSL) and pack sizes.

Acrivastine provides symptomatic relief in conditions believed to depend wholly or partly upon the triggered release of histamine. It is a potent competitive histamine H1 antagonist which lacks significant anti-cholinergic effects and has a low potential to penetrate the central nervous system. After oral administration of a single dose of 8 mg acrivastine to adults, the onset of actions, as determined by the ability to antagonise histamine induced weals and flares in the skin, is 15 minutes. Peak effects occur at 2 hours, and although activity declines slowly thereafter, significant inhibition of histamine induced weals and flares still occur 8 hours after dose. In patients, relief from the symptoms of allergic rhinitis is apparent within 1 hour after the systemic administration of the drug.

Acrivastine is well absorbed from the gut. In healthy adult volunteers, the peak plasma concentration (Cmax) is approximately 150 ng/ml, occurring at about 1.5 hours (Tmax) after the administration of 8 mg acrivastine. The plasma half-life is approximately 1.5 hours. In multiple dose studies over 6 days, no accumulation of acrivastine was observed. Renal excretion is the principal route of elimination of acrivastine.

A single centre, single dose, randomised, laboratory-blinded, crossover, two period, two sequence bioequivalence study conducted under fasting conditions was submitted to support these applications. The bioequivalence study is stated to have been conducted in accordance with Good Clinical Practice (GCP).

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

The MHRA has been assured that acceptable standards of Good Manufacturing Practice 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 or 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.
II QUALITY ASPECTS

II.1 Introduction
The finished product is presented as a hard capsule and each capsule contains 8 mg of acrivastine as the active ingredient. Other ingredients consist of the pharmaceutical excipients as follows: lactose monohydrate, sodium starch glycolate, magnesium stearate, titanium dioxide, gelatin and purified water.

Acrivastine Capsules are presented in aluminium/aluminium (Alu/Alu) and aluminium-polyvinyl chloride/polychlorotrifluoroethylene (Alu-PVC/ACLAR) blister packs containing either 7, 12, 21, 24 and 48 capsules for the pharmacy (P) medicine, Acrivastine 8 mg capsules, hard (PL 48468/0001); and 9, 12, 21 and 24 capsules for the GSL product' Brown & Burk Allergy Relief 8mg capsules, hard (PL 48468/0002). 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: Acrivastine
Chemical name: \((E)-3-[(E)-1-(4-methylphenyl)-3-pyrrolidin-1-yl-prop-1-enyl]\) pyridine-2-yl)prop-2-enoic acid

Structure:

![Structure of Acrivastine]

Molecular formula: \(\text{C}_{22}\text{H}_{24}\text{N}_{2}\text{O}_{2}\)
Molecular weight: 348.43
Appearance: white to light cream-coloured powder
Solubility: Acrivastine is soluble in methylene chloride and chloroform, sparingly soluble in methanol, slightly soluble in ethanol and dimethyl formamide, practically insoluble in water, dimethylsulfoxide, n-hexane, isopropyl alcohol and acetone.

The active substance acrivastine is the subject of an active substance master file (ASMF).

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.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. 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 to support 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, capsules containing 8 mg of acrivastine that are generic versions of the reference products Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited). A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients and suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate and gelatin, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

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

Manufacture of the products

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 shown satisfactory results.

Finished Product Specifications

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. 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 products in the packaging proposed for marketing. The data from these studies, for all packaging presentations support a shelf life of 2 years, with the storage conditions of ‘Do not store above 30°C. Store in the original package.’

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 these applications from a pharmaceutical viewpoint.

### III NON-CLINICAL ASPECTS

#### III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of acrivastine 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.

#### Impurities
A risk assessment has been provided for elemental impurities (in line with the ICH Q3D guideline) covering Class 1 and Class 2A elements based on declarations from the suppliers of the product components. The expected levels of elemental impurities are well below the permitted daily exposures for each element.

#### III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Acrivastine Capsules 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
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 acrivastine 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 acrivastine.

Acrivastine Capsules can be considered bioequivalent to the reference medicinal product; Benadryl Allergy Relief (PL 15513/0035 and PL 15513/0128; McNeil Products Limited).

#### IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

A single centre, single dose, randomised, laboratory-blinded, crossover, two-period, two-sequence comparative bioequivalence study of the applicant’s test product Acrivastine 8mg Capsules (Vivalabs Europe Limited) versus the reference product, Benadryl Allergy Relief (8 mg) Capsules (McNeil Products Limited) in healthy adult subjects under fasting conditions.
Following an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x 8 mg capsule) of the test or reference product (in each administration period) with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between each dose administration was 4 days.

Summary of pharmacokinetic results:

**Summary of Pharmacokinetic Parameters for Acrivastine 8mg ODT**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-t (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Formulation-T</strong></td>
<td>31</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Mean</td>
<td>1.105</td>
<td>213.134</td>
<td>637.447</td>
</tr>
<tr>
<td>SD</td>
<td>0.2935</td>
<td>38.9705</td>
<td>127.2231</td>
</tr>
<tr>
<td>CV(%)</td>
<td>26.6</td>
<td>18.3</td>
<td>20.0</td>
</tr>
<tr>
<td>Geometric Mean</td>
<td>1.069</td>
<td>209.676</td>
<td>625.552</td>
</tr>
<tr>
<td><strong>Reference Formulation-R</strong></td>
<td>31</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Mean</td>
<td>1.056</td>
<td>207.146</td>
<td>607.753</td>
</tr>
<tr>
<td>SD</td>
<td>0.2301</td>
<td>39.3715</td>
<td>123.1684</td>
</tr>
<tr>
<td>CV(%)</td>
<td>21.8</td>
<td>19.0</td>
<td>20.3</td>
</tr>
<tr>
<td>Geometric Mean</td>
<td>1.034</td>
<td>203.245</td>
<td>596.125</td>
</tr>
</tbody>
</table>

ANOVA p-value

- ln-transformed Formulation - 0.2978 0.0067
- Sequence - 0.6004 0.4675
- Period - 0.0555 0.0172
- Subject (Seq) - <0.0001 <0.0001

Geometric Least Squares Means

- ln-transformed Test-T - 209.539 625.261
- Reference-R - 203.474 596.629

Ratio of Geometric Least Squares Means(%) (T/R)

- ln-transformed - 103.0 104.8

Intra Subject Variability(%)

- ln-transformed - 10.9 6.3

90% Confidence Interval (T Vs. R)

- ln-transformed Lower - 98.25 101.98
- Upper - 107.94 107.70
- Power (%) - 100.0 100.0
Study conclusion

The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for acrivastine 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; Acrivastine 8mg Capsules (Vivalabs Europe Limited) and the reference product, Benadryl Allergy Relief (8 mg) Capsules (McNeil Products Limited) are bioequivalent.

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 Acrivastine Capsules.

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

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>• Hypersensitivity</td>
</tr>
<tr>
<td>• Patients with significant renal impairment</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>• Concomitant administration of alcohol and other CNS depressants</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>• Use during pregnancy and lactation</td>
</tr>
<tr>
<td>• Use in the elderly</td>
</tr>
</tbody>
</table>

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

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

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, as amended. 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.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. 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 (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 these medicines are presented below:
Acrivastine 8mg Capsules, hard and Brown & Burk Allergy Relief 8mg capsules, hard

Carton Size: 94(L) x 21(W) x 61(H) mm

Braille Reads
Acrivastine
#8mg
Capsules, hard
<table>
<thead>
<tr>
<th>Acrivastine 8mg Capsules, hard</th>
<th>Acrivastine 8mg Capsules, hard</th>
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<tbody>
<tr>
<td>Vivalabs Europe Limited</td>
<td>Vivalabs Europe Limited</td>
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<tr>
<td>Vivalabs Europe Limited</td>
<td>Vivalabs Europe Limited</td>
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</tbody>
</table>

Blister Size: 87 x 53 mm
Foil Width: 184 mm
Continuous Printing
PAR Acrivastine 8mg Capsules, hard and Brown & Burk Allergy Relief 8mg capsules, hard

Brown & Burk Allergy Relief 8mg capsules, hard

Carton Size: 94(L) x 21(W) x 61(H) mm

Braille Reads

Brown & Burk Allergy Relief
#8mg capsules, hard
Annex 1

Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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