Public Assessment Report

UKPAR

Aceteff 600mg Effervescent Tablets

(Acetylcysteine)

UK Licence No: PL 42286/0001

Dunelm Pharmaceuticals Limited
LAY SUMMARY

Aceteff 600mg Effervescent Tablets

(Acetylcysteine)

This is a summary of the Public Assessment Report (PAR) for Aceteff 600mg Effervescent Tablets (PL 42286/0001). It explains how the application for Aceteff 600mg Effervescent Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Aceteff 600mg Effervescent Tablets.

For practical information about using Aceteff 600mg Effervescent Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Aceteff Effervescent Tablets’ in this Lay summary.

What are Aceteff Effervescent Tablets and what are they used for?
Aceteff Effervescent Tablets are a generic medicine. This means that Aceteff Effervescent Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany).

Aceteff Effervescent Tablets are used for problems with the breathing passages (also known as the respiratory tract).

How do Aceteff Effervescent Tablets work?
Aceteff Effervescent Tablets contain the active ingredient acetylcysteine, which belongs to a group of medicines called ‘mucolytics’. Sometimes too much mucus (phlegm) is made or the phlegm is too sticky. The tablets work by making mucus/phlegm thinner and less sticky, which makes the mucus easier to cough up.

How are Aceteff Effervescent Tablets used?
This medicine can only be obtained with a prescription.

Aceteff Effervescent Tablets are taken by mouth. This medicine should be dissolved completely in a glass of water before use and the patient should drink the entire contents of the glass. Aceteff Effervescent Tablets should be taken after food.

The patient should always take Aceteff Effervescent Tablets exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if unsure.

The recommended dose is given in the table below:

<table>
<thead>
<tr>
<th>Age</th>
<th>Single dose</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents over 14 and</td>
<td>One tablet once</td>
<td>One tablet (equivalent to 600mg acetylcysteine)</td>
</tr>
<tr>
<td>adults</td>
<td>a day</td>
<td></td>
</tr>
</tbody>
</table>

Aceteff Effervescent Tablets are not suitable for children under 14 years of age.

Please read the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.
What benefits of Aceteff Effervescent Tablets have been shown in studies?
No additional clinical studies were needed as Aceteff Effervescent Tablets are a generic medicine that is given as an oral solution and contains the same active substance as the reference medicine, Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany).

What are the possible side effects of Aceteff Effervescent Tablets?
As Aceteff Effervescent Tablets are a generic, the benefits and possible side effects are taken as being the same as those of the reference medicine, Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany).

For the full list of all side effects reported with Aceteff Effervescent Tablets, see Section 4 of the package leaflet.

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

Why are Aceteff Effervescent Tablets approved?
In accordance with the EU requirements, Aceteff Effervescent Tablets have been shown to be comparable to the reference product Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany). Based on this evaluation, the MHRA concluded that the benefits of Aceteff Effervescent Tablets outweigh the identified risks and recommended Aceteff Effervescent Tablets for approval.

What measures are being taken to ensure the safe and effective use of Aceteff Effervescent Tablets?
A Risk Management Plan has been developed to ensure that Aceteff Effervescent Tablets are used as safely as possible. The relevant safety information has been included in the Summary of Product Characteristics and the package leaflet for Aceteff Effervescent 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 Aceteff Effervescent Tablets
A Marketing Authorisation was granted in the UK to Dunelm Pharmaceuticals Limited on 24 October 2016.

The Marketing Authorisation was granted with the name Siran 600mg Effervescent Tablets. Following the grant of a variation application on 22 February 2017, the name has changed to Aceteff 600mg Effervescent Tablets.

The full PAR for Aceteff Effervescent Tablets follows this summary.

This summary was last updated in May 2017.
SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Dunelm Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Aceteff 600 mg Effervescent Tablets (PL 42286/0001) on 24 October 2016. The product is a prescription only medicine (POM), indicated for mucolytic therapy for adjunctive therapy of respiratory tract disorders associated with excessive, viscous mucous secretions in adults and adolescents 14 years of age and over.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The application refers to the European Reference Product (ERP) Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany), which was first granted a licence in Germany on 22 April 1988.

Aceteff 600 mg Effervescent Tablets contain the active ingredient, acetylcysteine, which has been in widespread clinical use as a mucolytic agent since the 1960s. The mucolytic activity of acetylcysteine is most likely related to the splitting of disulphide bonds in mucus proteins, thereby altering the structure and disrupting ligand bonds to form smaller protein units. Acetylcysteine has additional pharmacodynamic effects including anti-oxidant effects due to its action as a scavenger of reactive oxygen species and as a precursor to glutathione following deacetylation to L-cysteine. Acetylcysteine has also been reported to inhibit JNK and MAP kinases and also NF-κB transcriptional pathways, involved in oxidative stress and inflammation. It therefore has potential for pleiotropic actions in respiratory disease.

No new non-clinical or clinical data were 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.

As the product meets the criteria regarding oral solutions specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), bioequivalence studies were not required.

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 the product.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking the proposed doses of Aceteff Effervescent Tablets, in the listed conditions, outweigh the risks.

The Marketing Authorisation was granted with the name Siran 600mg Effervescent Tablets. Following the grant of a variation application on 22 February 2017, the name has changed to Aceteff 600mg Effervescent Tablets.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

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

Aceteff 600 mg Effervescent Tablets are circular white tablets, approximately 18mm in diameter.

Each effervescent tablet contains 600 mg of the active substance acetylcysteine. The product also contains pharmaceutical excipients, namely sodium hydrogen carbonate, anhydrous citric acid, aspartame (E951) and lemon flavouring. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in white polypropylene tubes, each with a low density polyethylene tamper evident cap with integrated desiccant. The product is packed in pack sizes of 10, 20 and 30 (2x15) effervescent tablets.

Not all pack sizes may be marketed.

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

II.2 DRUG SUBSTANCE

Acetylcysteine
INN: Acetylcysteine
Chemical name: (2R)-2-(Acetylamino)-3-sulfanylpropanoic acid
N-Acetyl-L-Cysteine

Structure:

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{N} \quad \text{H} \\
\text{HS} & \quad \text{CO}_2\text{H}
\end{align*}
\]

Molecular formula: C₅H₉NO₃S
Mₚ: 163.2 g/mol
Appearance: A white or almost white, crystalline powder or colourless crystals.
Solubility: Freely soluble in water and in ethanol (965), practically insoluble in methylene chloride.

Acetylcysteine is the subject of a British Pharacopoeia monograph.

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

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, effervescent tablet that was bioequivalent to the reference product Fluimucil long 600 mg Effervescent Tablets (Zambon GmbH, Germany).
Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product. The *in-vitro* dissolution profiles were satisfactory.

With the exception of lemon flavouring, which is controlled to a suitable in-house specification, all the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

**Control of Finished Product**

The finished product specification is acceptable. The test methods have been described and have been validated adequately. 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 finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the special storage conditions ‘Store in original packaging to protect the contents from light and moisture. Do not store above 25°C. Re-seal tubes immediately after removing tablets.’ has been accepted.

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

**Bioequivalence/Bioavailability**

A bioequivalence study was not required to support an application of this type.

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

It is recommended that a Marketing Authorisation is granted for the application for Aceteff 600 mg Effervescent Tablets, from a quality point of view.

**III NON-CLINICAL ASPECTS**

**III. 1 Introduction**

The pharmacodynamic, pharmacokinetic and toxicological properties of acetylcysteine are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview 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
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Since Aceteff 600 mg Effervescent Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Aceteff 600 mg Effervescent Tablets, from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of acetylcysteine is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application.

A bioequivalence study was not submitted and none was required as the product meets the criteria regarding oral solutions specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference product. The excipients are not expected to affect the gastrointestinal transit, absorption or in vivo stability of the active substance.

IV.2 Pharmacokinetics
The pharmacokinetic properties of acetylcysteine are well known and are adequately described in the applicant’s non-clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of acetylcysteine are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of acetylcysteine is well-known. No new efficacy data are presented and none are required for this type of application.

IV.5 Clinical Safety
The clinical safety of acetylcysteine is well-known. No new efficacy data are presented and none are required for this type of application.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan, 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 Aceteff 600 mg Effervescent Tablets. A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>• Hypersensitivity to acetylcysteine or to any of the excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Use in children under 14 years of age</td>
</tr>
<tr>
<td></td>
<td>• Acetylcysteine induced bronchospasm in patients with asthma</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of GI haemorrhage in patients with a history of ulcers</td>
</tr>
<tr>
<td></td>
<td>• Inhibition of diamine oxidase in patients with intolerance to histamines</td>
</tr>
<tr>
<td></td>
<td>• Use in patients on a low sodium diet</td>
</tr>
<tr>
<td></td>
<td>• Use in patients with phenylketonuria</td>
</tr>
<tr>
<td></td>
<td>• Drug interactions: Antibiotics, antitussives and nitroglycerin</td>
</tr>
<tr>
<td></td>
<td>• Interaction with laboratory tests: colorimetric assay of salicylates and determination of ketone bodies in urinalysis</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>• Decrease in platelet function</td>
</tr>
<tr>
<td></td>
<td>• Severe skin reactions</td>
</tr>
<tr>
<td></td>
<td>• Possible increased rate of adverse drug reactions in patients with renal or hepatic impairment</td>
</tr>
<tr>
<td>Missing information</td>
<td>• Use in pregnancy and breast feeding</td>
</tr>
</tbody>
</table>

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

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Aceteff 600 mg Effervescent Tablets, from a clinical point of view.

V USER CONSULTATION
A 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 pack 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 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 an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of acetylcysteine are well-known, no additional data were required.

EFFICACY
No new efficacy data have been submitted and none are required for this type of application.

SAFETY
The safety profile of acetylcysteine is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE
The SmPC, patient information leaflet (PIL) and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with acetylcysteine is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the authorised reference product. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Aceteff™ 600mg Effervescent Tablets
Acetylcysteine

Each effervescent tablet contains 600mg acetylcysteine. Also contains aspartame and sodium (as sodium hydrogen carbonate). See leaflet for further information.

Store in the original packaging to protect the contents from light and moisture. Do not store above 25°C. Reseal tube immediately after removing a tablet.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

MA Holder: Dunelm Pharmaceuticals Limited
28 Georges Street, Drogheda, County Louth, Ireland

Aceteff is a trade mark of Dunelm Pharmaceuticals Limited

Pl 42286/0001
Aceteff™ 600mg
Effervescent Tablets
Acetylcysteine

20 Tablets for oral use.
Each effervescent tablet contains 600mg
acetylcysteine. Also contains aspartame and
sodium (as sodium hydrogen carbonate).
See leaflet for further information. Read the
package leaflet before use. Effervescent tablets
to be taken dissolved in water. Use as directed by
your doctor.
KEEP OUT OF THE REACH AND SIGHT OF
CHILDREN.

DUNELM
Pharmaceuticals Ltd
MA Holder: Dunelm Pharmaceuticals Limited
28 Georges Street, Drogheda,
County Louth, Ireland

Store in the original packaging to protect the
contents from light and moisture.
Do not store above 25°C.
Reseal tube immediately after removing a tablet.

POM PL 42286/0001

Batch No./Expiry Date: see bottom of the tube.
Aceteff 600mg Effervescent Tablets

Acetylcysteine

Each effervescent tablet contains 600mg acetylcysteine. Also contains aspartame and sodium (as sodium hydrogen carbonate). See leaflet for further information.

DUNELM Pharmaceuticals Ltd

30 Tablets for oral use

Store in the original packaging to protect the contents from light and moisture. Do not store above 25°C. Reseal tube immediately after removing a tablet. Effervescent tablets to be taken dissolved in water. Use as directed by your doctor. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Acetylcysteine

Aceteff 600mg Effervescent Tablets

PL 42286/0001

MA Holder: Dunelm Pharmaceuticals Limited

25 College Street, Drogheda, County Louth, Ireland.
Aceteff™ 600mg Effervescent Tablets
Acetylcysteine

15 Tablets for oral use.
Each effervescent tablet contains 600mg acetylcysteine. Also contains aspartame and sodium (as sodium hydrogen carbonate). See leaflet for further information. Read the package leaflet before use. Effervescent tablets to be taken dissolved in water. Use as directed by your doctor.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

DUNELM Pharmaceuticals Ltd
MA Holder: Dunelm Pharmaceuticals Limited
28 Georges Street, Drogheda,
County Louth, Ireland

Store in the original packaging to protect the contents from light and moisture.
Do not store above 25°C.
Reseal tube immediately after removing a tablet.

POM PL 42286/0001

Batch No./Expiry Date: see bottom of the tube.
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)

The following table lists non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the 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>03/03/2016</td>
<td>Type IB</td>
<td>To update and correct section 4.1 of the summary of product characteristics (SmPC) as it has a typographical error and does not correctly reflect the wording as proposed by the MHRA in a request for further information (RFI) dated May 2016, prior to grant of the marketing authorisation (MA) for this product.</td>
<td>Approved on 05 April 2017</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 42286/0001 - 0003

Product: Aceteff 600mg Effervescent Tablets

Marketing Authorisation Holder: Dunelm Pharmaceuticals Limited

ActiveIngredient: acetylcysteine

Reason: To update and correct section 4.1 of the summary of product characteristics (SmPC) as it has a typographical error and does not correctly reflect the wording as proposed by the MHRA in an request for further information (RFI) dated May 2016, prior to grant of the MA for this product.

Supportingevidence The applicant has submitted updated section of the SmPC.

Evaluation The amended section 4.1 of the SmPC is satisfactory.

Conclusion The updated SmPC fragment has been incorporated into this Marketing Authorisation. The proposed change is acceptable.

Decision: Grant
Date: 05 April 2017