Public Assessment Report

Decentralised Procedure

Butamirate 7.5mg/5ml Syrup
(butamirate citrate)

Procedure No: UK/H/5574/001/DC

UK Licence No: PL 30306/0497

Actavis Group PTC ehf
**LAY SUMMARY**

**Butamirate 7.5mg/5ml Syrup**
**(butamirate citrate)**

This is a summary of the Public Assessment Report (PAR) for Butamirate 7.5mg/5ml Syrup (PL 30306/0497; UK/H/5574/001/DC). It explains how the application for Butamirate 7.5mg/5ml Syrup 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 Butamirate 7.5mg/5ml Syrup.

For practical information about using Butamirate 7.5mg/5ml Syrup, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Butamirate Syrup’ in this report.

**What is Butamirate Syrup and what is it used for?**

Butamirate Syrup is a generic medicine. This means that Butamirate Syrup is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Sinecod, 0,15%, sirop (Novartis Consumer Health S.A.), which was authorised in Belgium in May 2000.

Butamirate Syrup is used in adults (18 years and older), for the symptomatic treatment of non-productive (dry) cough.

**How does Butamirate Syrup work?**

Butamirate Syrup contains the active ingredient butamirate (as butamirate citrate), which belongs to a group of medicines called antitussives. Butamirate Syrup inhibits the cough reflex.

**How is Butamirate Syrup used?**

Butamirate Syrup is taken by mouth.

This medicine should always be taken exactly as described in the package leaflet or as instructed by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if he/she is not sure.

The recommended dose in adults is 15ml up to 4 times daily. The measuring cup packaged with the Butamirate Syrup should be used for proper dosing.

Butamirate Syrup should not be used in children or adolescents under 18 years of age.

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

Butamirate Syrup can only be obtained with a prescription.

**What benefits of Butamirate Syrup have been shown in studies?**

As Butamirate Syrup is a generic medicine, studies in patients have been limited to tests to determine that it is similar to the reference medicine, Sinecod, 0,15%, sirop (Novartis Consumer Health S.A.). Two medicines are considered to be bioequivalent when they produce the same levels of the active substance in the body.

In addition, Actavis Group PTC ehf provided data from the published literature on butamirate citrate.
What are possible side effects of Butamirate Syrup?
Like all medicines, Butamirate Syrup can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Butamirate Syrup, see section 4 of the package leaflet.
For the full list of restrictions, see the package leaflet for Butamirate Syrup.

Why is Butamirate Syrup approved?
The MHRA concluded that, in accordance with EU requirements, the benefits outweigh the identified risks and recommended that Butamirate Syrup be approved for use.

What measures are being taken to ensure the safe and effective use of Butamirate Syrup?
A risk management plan has been developed to ensure that Butamirate Syrup is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Butamirate Syrup, 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 as well.

Other information about Butamirate Syrup.
Denmark, Finland, Iceland, Norway, Poland, Sweden, Romania, Malta and Cyprus and the UK agreed to grant a Marketing Authorisation for Butamirate Syrup on 02 April 2015. A Marketing Authorisation was granted in the UK on 30 April 2015.

The full PAR for Butamirate Syrup follows this summary.

For more information about treatment with Butamirate Syrup, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2015.
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Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Butamirate 7.5 mg/5ml Syrup (PL 30306/0497; UK/H/5574/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for the symptomatic treatment of non-productive cough. The product may be referred to as Butamirate Syrup in this report.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Cyprus, Denmark, Finland, Iceland, Malta, Norway, Poland, Romania and Sweden as Concerned Member States (CMS). The application for Butamirate 7.5 mg/5ml Syrup was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application cross-referring to Sinecod, 0.15%, sirop (Novartis Consumer Health S. A.) which has been authorised since May 2000 in Belgium.

The active ingredient, butamirate citrate, is an antitussive substance that influences and inhibits the cough reflex in inflammatory processes underlying dry non-productive cough, but does not belong to the group of opiate alkaloids. It is considered that butamirate citrate is a centrally acting drug although its exact mechanism is not completely clear. It exerts non-specific anticholinergic and bronchospasmytic effects thereby improving respiratory function. Butamirate does not induce tolerance or dependence. It has a wide therapeutic index.

No new non-clinical or 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. A bioequivalence study was not necessary to support this application for an oral solution.

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 manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 207) on 02 April 2015. After a subsequent national phase, a licence was granted in the UK on 30 April 2015.

II  QUALITY ASPECTS
II.1 Introduction
The application was submitted in accordance with Article 10(1) of Directive 2001/83/EC, as amended.

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

The product is available as a colourless or pale yellow liquid.

Each 1 ml of syrup contains 1.5 mg butamirate citrate equivalent to 0.924 mg butamirate. Each 5 ml of syrup contains 7.5 mg butamirate citrate equivalent to 4.62 mg butamirate.

The other ingredients consist of the pharmaceutical excipients sorbitol (E420), glycerol, sucralose (E955), sodium benzoate (E211), citric acid monohydrate, caramel flavour 12788 (containing flavouring substances, flavouring preparations, natural flavouring substances and propylene glycol (E1520)), mix chocolate 70244 (containing flavouring preparations, flavouring substances, natural flavouring substances, smoke flavourings, propylene glycol (E1520), water, quinine hydrochloride, dextrose, and quassin) and purified water. Appropriate justification for the inclusion of each excipient has been provided.
The finished product is supplied in 100 ml or 200 ml amber glass or polyethylene terephthalate bottles with child-resistant polypropylene/polyethylene screw caps. Each pack contains a polypropylene measuring cup graduated for dosing of 5 ml, 10 ml, 15 ml, 20 ml, 25 ml and 30 ml.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance

Butamirate citrate

International Non-proprietary Name (INN): Butamirate citrate
Pharmacopoeia Bohemica: Butamirati citras
Chemical name: 2-[2(diethylamino)ethoxy]-ethyl; 2-phenylbutyrate citrate
Chemical abstract Service registry number: 18109-81-4
Molecular formula: C_{24}H_{37}NO_{10}
Molecular mass: 499.56

Structural formula:

Description: A white or slightly yellowish crystalline powder, slightly waxy, slight amine odour.
Solubility: Sparsely soluble in water, soluble in 96% ethanol
Melting range: 74 – 78°C

Butamirate citrate is not the subject of a European Pharmacopoeia monograph.

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. 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 specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting 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 a safe, efficacious, stable, syrup containing butamirate citrate 7.5 mg/5ml that was comparable in performance/bioequivalent to the reference medicinal product Sinecod 0.15%, sirop, (Novartis Consumer Healthcare S.A.). Suitable pharmaceutical development data have been provided for this application.

All excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeia monographs, with the exception of caramel flavour 12788 and mix chocolate 70244, which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

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 at production scale and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation on future production-scale batches.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. 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 2 years has been approved for the unopened product and 6 months for the product once opened, with the special storage conditions ‘Do not store above 25°C.’

Suitable post approval stability commitments have been provided

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application for this aqueous oral solution product.

II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application for Butamirate 7.5mg/5ml Syrup.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

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:

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Butamirate 7.5mg/5ml Syrup
butamirate citrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1ml of syrup contains 1.5mg butamirate citrate.
5ml of syrup contains 7.5mg butamirate citrate.

3. LIST OF EXCIPIENTS

Contains sorbitol (E420) and glycerol.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Syrup
100ml
200ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
Butamirate 7.5mg/5ml Syrup

Do not store above 25°C.
Shelf-life after first opening the bottle: 6 months

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0497

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>
1. **NAME OF THE MEDICINAL PRODUCT**

Butamirate 7.5mg/5ml Syrup
butamirate citrate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1ml of syrup contains 1.5mg butamirate citrate.
5ml of syrup contains 7.5mg butamirate citrate.

3. **LIST OF EXCIPIENTS**

Contains sorbitol (E420) and glycerol.
See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Syrup
100ml
200ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Read the package leaflet before use.
Use as directed by your doctor.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**
Butamirate 7.5mg/5ml Syrup

Do not store above 25°C.
Shelf-life after first opening the bottle: 6 months

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0497

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

For relief of dry cough.

The recommended dose is:
Adults: 15ml up to 4 times daily

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

butamirate 7.5mg/5ml syrup
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of butamirate citrate are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

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
The pharmacology of butamirate citrate is well known and is adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of butamirate citrate are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of butamirate citrate are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
Butamirate 7.5mg/5ml Syrup is intended for generic substitution, however as it has not previously been marketed in all the Member States, an increased exposure to the environment is expected.

In response to objections raised, the applicant has provided an updated ERA with a Phase I Estimation of Exposure assessment. The results from the Phase I Estimation of Exposure assessment indicates that butamirate citrate does not require further testing as per the guideline, and that it poses no additional risk to the environment.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Butamirate 7.5mg/5ml Syrup, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The product is a generic medicinal product as defined by article 10(1) of Directive 2001/83/EC, as amended, with the reference product being Sinecod, 0.15%, sirop, (Novartis Consumer Healthcare S.A.), which was granted in Belgium in May 2000. In accordance with current CHMP guidelines, no new bioequivalence, efficacy or safety study data are required to support this application as Butamirate Syrup, which is an aqueous solution, satisfies the criteria of having the same quantitative and qualitative composition with the same pharmaceutical form when compared with the reference product.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The pharmacokinetic properties of butamirate citrate 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 butamirate citrate 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 butamirate citrate is well-known. No new efficacy data were submitted and none are required for this application for an oral solution.

IV.5 Clinical Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this 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 Butamirate Syrup.

The MAH identified the following as safety concerns:

<table>
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<th>Summary of safety concerns</th>
<th>Concomitant use with expectorants</th>
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<tbody>
<tr>
<td>Important identified risks</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Use in children under 3 years of age</td>
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<tr>
<td>Important potential risks</td>
<td>NA</td>
</tr>
<tr>
<td>Important missing information</td>
<td>Use during pregnancy</td>
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<td></td>
<td>Use during breastfeeding</td>
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<td></td>
<td>Use in patients with renal or hepatic impairment</td>
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<td></td>
<td>Drug interactions</td>
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</table>

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

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

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 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 AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Butamirate 7.5mg/5ml Syrup 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 butamirate citrate are well-known, no additional data were required.
EFFICACY
The clinical efficacy of butamirate citrate is well-known.

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

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

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
### 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)*

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<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</th>
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Y/N (version)