Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Benzylpenicillin benzathine 0.6, 1.2 and 2.4 Million I.U. powder and solvent for suspension for injection

(benzylpenicillin benzathine)

Product Lincence Numbers: PL 41542/0005-7

Brancaster Pharma Limited

LAY SUMMARY

Benzylpenicillin benzathine 0.6, 1.2 and 2.4 Million I.U. powder and solvent for suspension for injection

(benzylpenicillin benzathine)

This is a summary of the Public Assessment Report (PAR) for Benzylpenicillin benzathine 0.6, 1.2 and 2.4 Million I.U. powder and solvent for suspension for injection. It explains how Benzylpenicillin benzathine 0.6, 1.2 and 2.4 Million I.U. powder and solvent for suspension for injection were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Benzylpenicillin benzathine in this lay summary for ease of reading.

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

What is Benzylpenicillin benzathine and what is it used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Extencilline 0.6 MIU, 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection.

Benzylpenicillin benzathine is used for the treatment of:

• erysipelas (skin infection)
• syphilis
• tropical infectious diseases of the skin, caused by bacteria of the Treponema species, such as yaws or pinta

Benzylpenicillin benzathine is also used to prevent the following diseases:

• rheumatic fever
• poststreptococcal glomerulonephritis (a specific form of kidney inflammation)
• erysipelas (skin infection)

How does Benzylpenicillin benzathine work?
This medicine contains the active ingredient benzylpenicillin benzathine, which is one of a group of medicines known as penicillins (“antibiotics”). Antibiotics are used to kill the bacteria (germs) which cause infections.

How is Benzylpenicillin benzathine used?
The pharmaceutical form of this medicine is powder and solvent for suspension for injection and the route of administration is intramuscular.

The injection must not be administered into tissue with poor blood flow. In case of repeated intramuscular application, the site of injection must be changed. Severe local reactions may occur during intramuscular administration, especially in young children. For this reason, other treatments such as a different penicillin formulation can be used where possible.

General therapy:
- Adults and adolescents: 1.2 Million I.U.
- Children (> 30 kg body weight): 1.2 Million I.U.
- Children (< 30 kg body weight): 0.6 Million I.U.

Treatment of syphilis:
- Primary and secondary stage

- Adults and adolescents: 2.4 Million I.U.
- Children: 50,000 IU per kg body weight; however not more than 2.4 Million I.U.

Duration of treatment: Single dose
(if clinical symptoms return or laboratory findings remain strongly positive, treatment should be repeated.)

- Late-stage syphilis (latent seropositive syphilis)

- Adults and adolescents: 2.4 Million I.U.
- Children: 50,000 IU per kg body weight, but not more than 2.4 Million I.U.

Duration of treatment: Once weekly for 3 weeks

- Treatment of congenital syphilis (without neurological involvement)

- Newborns and infants: 50,000 IU per kg body weight
Duration of treatment: Single dose

Treatment of tropical infectious skin diseases (yaws and pinta):
- Adults and adolescents: 1.2 Million I.U.
- Children (> 30 kg body weight): 1.2 Million I.U.
- Children (< 30 kg body weight): 0.6 Million I.U.

Duration of treatment: Single dose

Prevention of rheumatic fever, poststreptococcal glomerulonephritis and erysipelas:
- Adults and adolescents: 1.2 Million I.U.
- Children (> 30 kg body weight): 1.2 Million I.U.
- Children (< 30 kg body weight):

Duration of treatment: 0.6 Million I.U.
a) without heart involvement: at least 5 years, or up to 21 years of age every 3-4 weeks.
b) temporary heart involvement: at least 10 years, or up to 21 years of age every 3-4 weeks.
c) persistent heart involvement: at least 10 years or up to 40 years of age every 3-4 weeks; life-long treatment is sometimes necessary.

Special patient groups (impaired kidney function or impaired liver function)
The dosage and dosing interval will be determined by a doctor. If patients have any questions on the dosage, they should contact a doctor.

For further information on how Benzylpenicillin benzathine is 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 only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Benzylpenicillin benzathine have been shown in studies?
Benzylpenicillin benzathine is a generic medicine that fulfils criteria meaning that no additional studies are required. Benzylpenicillin benzathine has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the PAR.

What are the possible side effects of Benzylpenicillin benzathine?
Because Benzylpenicillin benzathine is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why was Benzylpenicillin benzathine approved?
It was concluded that, in accordance with EU requirements, Benzylpenicillin benzathine has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Benzylpenicillin benzathine?
A Risk Management Plan (RMP) has been developed to ensure that Benzylpenicillin benzathine is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Benzylpenicillin benzathine
Marketing Authorisations for Benzylpenicillin benzathine were granted in the UK on 24 July 2019.

The full PAR for Benzylpenicillin benzathine follows this summary.

This summary was last updated in September 2019.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Benzylpenicillin benzathine 0.6, 1.2 and 2.4 Million I.U. powder and solvent for suspension for injection (PL 41542/0005-7) could be approved.

The product is indicated in adults, adolescents, children and neonates for the treatment and prophylaxis of the following infections:

For the treatment of:
- erysipelas
- syphilis: early syphilis (primary and secondary)
- latent syphilis (except for neurosyphilis and presence of pathological CSF findings)
- yaws
- pinta
-

For the prophylaxis of:
- rheumatic fever (chorea, rheumatic carditis)
- poststreptococcal glomerulonephritis
- erysipelas

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

These products contain the active substance benzylpenicillin benzathine. the mechanism of action is based on an inhibition of bacterial cell wall synthesis (during the growth phase) through a blockade of the penicillin-binding proteins (PBPs), such as transpeptidases. This results in a bactericidal action.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines. The reference medicinal products are Extencilline 0.6 MIU, 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection, which were first granted in the EU to France on 21 March 1983.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being a generic medicinal products of reference products that have been licensed for over 10 years.

A biowaiver was submitted with these applications, which was accepted. No bioequivalence study was required and no new clinical studies were provided with these applications.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

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

Advice was sought from the Commission of Human Medicines (CHM) on 22 May 2018 due to the applicant being unable to provide sufficient information to demonstrate the quality,

efficacy and safety of the product. The applicant submitted further evidence to address the concerns.

Marketing authorisations were granted for these products on 24 July 2019.

II QUALITY ASPECTS

II.1 Introduction

These products consist of powder and solvent for suspension for injection.

In addition to benzylpenicillin benzathine, these products also contain the excipients soya lecithin, polysorbate 80, carmellose sodium, sodium citrate, anhydrous and povidone making up the powder, and water for injections as a solvent.

The finished products are packaged in powder vials and glass ampoules of solvent for suspension of injection in a carton. The pack sizes are 1 vial and 1 glass ampoule of solvent.

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.

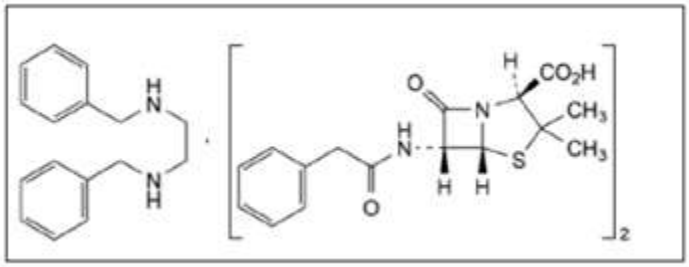
II.2 ACTIVE SUBSTANCE

rINN: Benzylpenicillin benzathine

Chemical Name: N,N´-Dibenzylethane-1,2-diamine compound (1:2) with (2S,5R,6R)-3,3-dimethyl-7oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0.]heptane-2-carboxylic acid

Molecular Formula: $C_{48}H_{56}N_6O_8S_2$

Chemical Structure:



Molecular Weight: 909 g/mol

Appearance: White or almost-white powder.

Solubility: Very slightly soluble in water, freely soluble in dimethylformamide and in formamide, slightly soluble in ethanol.

Benzylpenicillin benzathine is the subject of a European Pharmacopoeia monograph.

A Certificate of Suitability was not provided to support this application.

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 specifications 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. Batch analysis data are provided and 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 complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the manufacture of the products.

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

Manufacture of the products

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

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 and has shown satisfactory results.

Finished Product Specifications

The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months with no special storage conditions is acceptable.

Following reconstitution, the product should be used immediately.

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

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of benzylpenicillin benzathine 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.

III.2 Pharmacology

No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of benzylpenicillin benzathine are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for these applications and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Extencilline 0.6 MIU, 1.2 MIU and 2.4 MIU powder and solvent for suspension for injection.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Retarpen (AT/H/0582/001-003/MR) for the content and key safety messages and Bramox (NL/H/3123/001-002/DC) for the design and layout. The bridging report submitted by the MAH is acceptable.

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. Extensive clinical experience with benzylpenicillin benzathine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


Benzylpenicillin benzathine
0.6 Million I.U. powder and solvent for suspension for injection
Benzylpenicillin benzathine
If it is necessary
LOT
MFG
EXP
Data Matrix Area
Brancaster PHARMA

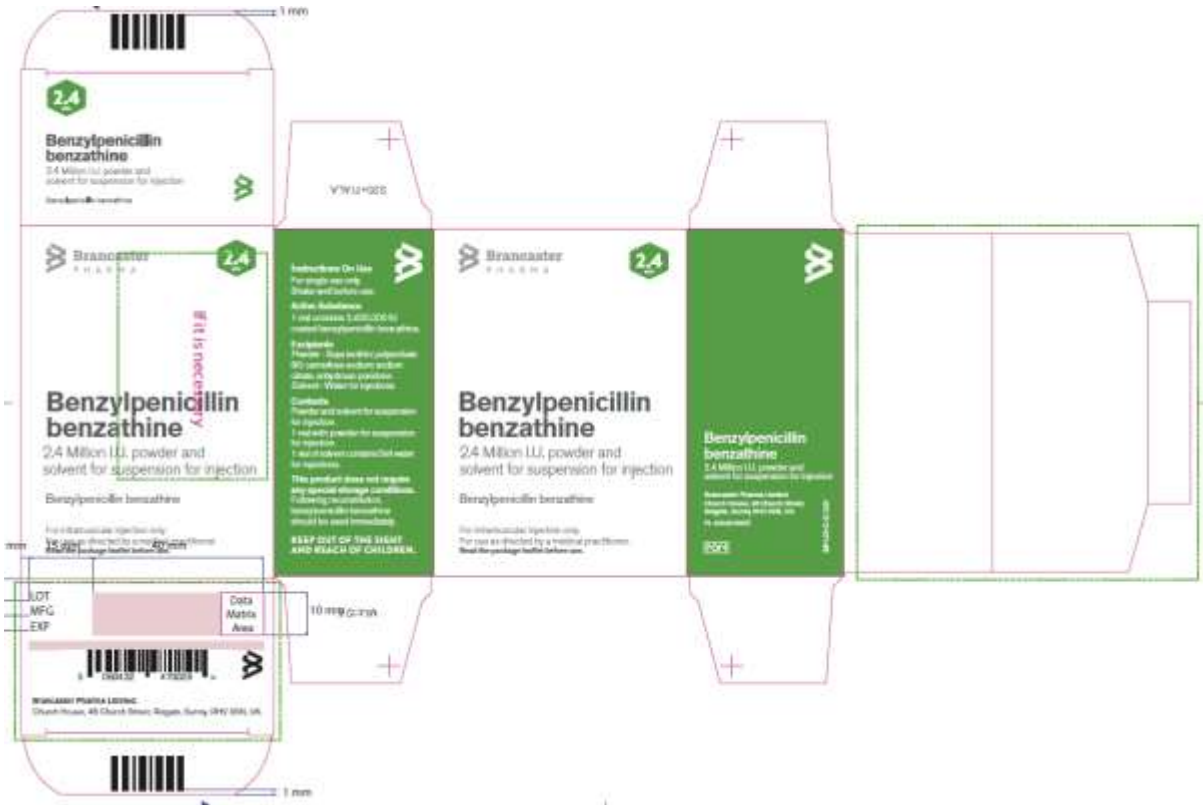

EXP
MFG
LOT
2 mm
Benzylpenicillin benzathine
0.6 Million I.U.
Powder and solvent for suspension for injection
For intramuscular injection only.
For single use only.
Shake well before use.
0.6
PL 41542/0005
POM
Brancaster PHARMA

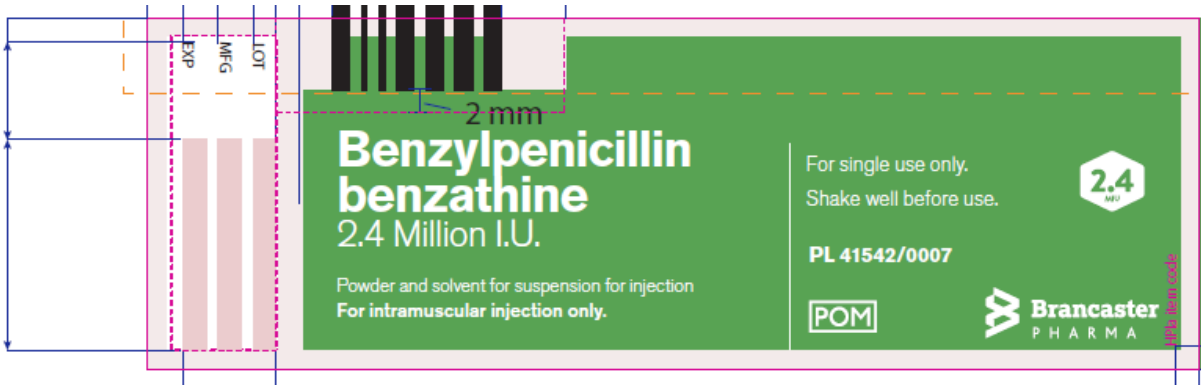

Water for Injections
5 ml
To be used for reconstitution.
Discard any unused solution.
Brancaster PHARMA
PL 41542/0005
POM


Benzylpenicillin benzathine
1.2 Million I.U. powder and solvent for suspension for injection
Benzylpenicillin benzathine
Brancaster PHARMA
LOT
MFG
EXP
Data Matrix Area


EXP
MFG
LOT
2 mm
Benzylpenicillin benzathine
1.2 Million I.U.
Powder and solvent for suspension for injection
For intramuscular injection only.
For single use only.
Shake well before use.
1.2
PL 41542/0006
POM
Brancaster PHARMA


Water for Injections
5 ml
To be used for reconstitution.
Discard any unused solution.
Brancaster PHARMA
PL 41542/0006
POM


Benzylpenicillin benzathine
2.4 Million I.U. powder and solvent for suspension for injection
Benzylpenicillin benzathine
Brancaster PHARMA
LOT
MFG
EXP
Data Matrix Area


EXP
MFG
LOT
2 mm
Benzylpenicillin benzathine
2.4 Million I.U.
Powder and solvent for suspension for injection
For intramuscular injection only.
For single use only.
Shake well before use.
2.4 MIU
PL 41542/0007
POM
Brancaster PHARMA


Water for Injections
5 ml
To be used for reconstitution.
Discard any unused solution.
Brancaster PHARMA
PL 41542/0007
POM

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Outcome**	**Assessment report attached Y/N**