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Public Assessment Report

Name of the Product:

Cefazolin AptaPharma
1 g
powder for solution for injection/infusion

(cefazolin sodium)

Procedure number: HU/H/0615/001/DC

Marketing authorisation holder: Apta Medica Internacional d.o.o.

Date: 18. 03. 2021.

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Cefazolin AptaPharma 1 g powder for solution for injection/infusion. The holder of the marketing authorisation is Apta Medica Internacional d.o.o.

The active substance is cefazolin sodium.

- Cefazolin AptaPharma 1 g powder for solution for injection/infusion: each vial contains 1048 mg cefazolin sodium equivalent to 1 g cefazolin.

The appearance of the powder is:
– The Cefazolin AptaPharma 1 g powder for solution for injection/infusion is white or almost white powder.

The solution has a pH in range 4.7 – 5.1 and an osmolality in range 308-675 mOsm/kg.

The powder is available in glass vials.

Cefazolin AptaPharma 1 g powder for solution for injection/infusion contains the active substance cefazolin sodium , which is an antibiotic. Cefazolin is used to treat bacterial infections caused by cefazolin-susceptible bacteria, e.g:
- Infections of skin and soft tissue
- Infections of bones and joints

Cefazolin can also be used before, during and after surgery to prevent possible infections.

What patients need to know before using Cefazolin AptaPharma

Patients must not use Cefazolin AptaPharma if they

- are allergic to cefazolin or for any other ingredient of this medicine;
- are allergic (hypersensitive) to any cephalosporin antibiotics;
- have ever had a severe allergic (hypersensitive) reaction to any other type of beta lactam antibiotic (penicillins, monobactams and carbapenems).

Warnings and precautions

Patients must talk to their doctor before taking Cefazolin AptaPharma if they
- are prone to allergic reactions (e.g. hay fever or bronchial asthma), since then the risk of severe allergic reactions to Cefazolin AptaPharma is increased;
- have had previously an allergic reaction to other beta-lactam antibiotics (e.g. penicillins), since then there is an increased risk of being allergic to Cefazolin AptaPharma as well;

- suffer from an impaired kidney or liver function;
- suffer from disorders of blood clotting (e.g. haemophilia) or their present condition can lead to such defects (parenteral feeding, malnutrition, liver or kidney diseases, reduction in blood platelets which increases risk of bleeding or bruising [thrombocytopenia], administration of medicines that prevent blood clotting [anticoagulants like heparin]);
- suffer from diseases which can cause bleedings (e.g. gastrointestinal ulcers);
- suffer from severe persistent diarrhoea during or after treatment with Cefazolin AptaPharma. In this case they must contact their doctor immediately;
- long-term or repeated treatment with cefazolin may lead to further infection by cefazolin resistant fungi or bacteria (superinfection).

Taking any anti-diarrhoea medicine without consulting the doctor is not allowed.

Children

Cefazolin AptaPharma may not be used in newborn infants and infants below the age of 1 month as the safety of use has not yet been established in this group

Other medicines and Cefazolin AptaPharma

Those who are taking, have recently taken or might take any other medicines, including medicines available without prescription, must consult their doctor.

The doctor will take special care if patients are using any of the following medicines:
Anticoagulants (medicines which prevent blood clotting):
Cefazolin AptaPharma may very rarely lead to disorders of blood clotting. Therefore, if patients simultaneously receive cefazolin and medicines that prevent blood clotting (e.g. heparin), a careful and regular control of the coagulation factors is necessary.

Probenecid (medicine for the treatment of joint disease and gout).

Medicines potentially harmful to kidney: Cefazolin AptaPharma may intensify the harmful effect of certain antibiotics (aminoglycosides) and of medicines that cause increase in urination (diuretics, e.g. furosemide) on the kidney. Using Cefazolin AptaPharma and one of these medicines at the same time requires regular monitoring of the kidney function, especially in patients with kidney disease.

Pregnancy and breast-feeding

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, doctor or nurse should be asked for advice before using this medicine.

Pregnancy
Cefazolin AptaPharma crosses the placenta and can affect the unborn child. Therefore, if patients are pregnant, the doctor should only give them cefazolin if clearly necessary and after careful consideration of benefits and risks.

Breast-feeding
Cefazolin AptaPharma passes in small amounts into breast milk. Therefore, breastfeeding should be discontinued during treatment with Cefazolin AptaPharma.

Driving and using machines

Cefazolin AptaPharma has no or negligible influence on the ability to drive and use machines.

Cefazolin AptaPharma contains sodium

This medicine contains approximately 2.2 mmol (approximately 50.6 mg) of sodium (main component of cooking/table salt) in each 1.0 g. This is equivalent to 2.5 % of the recommended maximum daily dietary intake of sodium for an adult, per 1,0 g dose which should be taken into consideration by patients on a controlled sodium diet.

How is Cefazolin AptaPharma administered

Cefazolin AptaPharma is always administered by healthcare personnel. It will be given as an injection or infusion (into a vein) after being dissolved, or into a muscle (intramuscularly) as a deep IM injection. The doctor will inform patients about the necessary duration and frequency of administration of Cefazolin AptaPharma.

Dosage

Adult patients with normal renal function
- Infections caused by bacteria susceptible to this medicine: 1 – 2 g daily, divided into 2 – 3 doses.
- Infections caused by bacteria less susceptible to this medicine: 3 – 4 g daily, divided into 3 – 4 doses.

- An increase of the daily dose up to 6 g in three or four equal doses is possible.

Use in children and adolescents

Prematures and infants below the age of one month:
The safety in infants below the age of one month has not been determined.

Children over the age of one month:
- Infections caused by bacteria susceptible to this medicine:
  25 – 50 mg / kg body weight / day divided in 2 – 4 single doses, every 6, 8 or 12 hours.
- Infections caused by bacteria less susceptible to this medicine: Up to 100 mg /kg body weight/day divided in 3 – 4 single doses, every 6 – 8 hours.

This product is not recommended for children under 1 month of life.

Elderly patients

No dosage adjustment is required for elderly patients with normal renal function.

Special dosage recommendations

Prevention of infections during surgical procedures
1 g cefazolin 30 - 60 minutes before surgery.
In case of long surgical procedures (2 hours or more), additional 0.5 g - 1 g cefazolin during the operation.

Patients with impaired kidney function
In patients with impairment of the kidney function, the elimination of cefazolin is slower. For this reason, their doctor will adjust the dosage according to the severity of the kidney impairment by reducing the maintenance dose or prolongation of the dosage intervals.

Duration of treatment
The treatment duration depends on the severity of the infection as well as on the recovery from your illness.

What to do if more Cefazolin AptaPharma was given that it should have been?

Since the medicine will be given to patients by a doctor or nurse, it is unlikely that they will be given too much.
Symptoms of overdose are headache, dizziness (vertigo), sensation of pricking or tingling on the skin (paraesthesia), restlessness (agitation), involuntary twitching of a muscle or a group of muscles (myoclonia) and cramps (convulsions). If these symptoms occur the doctor must be contacted immediately.
In emergencies, the physician must take the necessary measures for the treatment of symptoms of overdose.

What to do if giving Cefazolin AptaPharma was missed?

A double dose must not be given to make up for a forgotten dose. A forgotten dose should only be given before the next regular dose if the time until the next regular dose is long enough.

May patients stop using Cefazolin AptaPharma?

Low dosage, irregular administration or stopping the treatment too early can compromise the outcome of the therapy or lead to a relapse, that is more difficult to treat. Following the instructions of the doctor is necessary.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Patients must stop using this medicine and contact their doctor immediately if they notice any of these symptoms:

Uncommon: may affect up to 1 in 100 people
- redness of the skin (erythema), widespread skin rash (erythema multiforme or exanthema), hives (red, itchy, bumpy skin rash) on the surface of the skin (urticaria), fever, swelling beneath the skin (angioedema) and/or swelling of the lung tissue possibly with a cough and breathing difficulties (interstitial pneumonia or pneumonitis), as these side effects may indicate an allergic reaction to this medicine.

Rare: may affect up to 1 in 1000 people
- jaundice (yellow colour in the skin and whites of the eyes);
- severe skin rash with flushing, fever, blisters or ulcers (Stevens Johnson syndrome) or a severe rash with reddening, peeling and swelling of the skin that looks like a burn (toxic epidermal necrolysis).

Very rare: may affect up to 1 in 10,000 people
- a severe allergic reaction (anaphylactic shock) with breathing difficulty, swelling of the throat, face, eyelids or lips, increased heart rate and falling blood pressure. This reaction may start soon after the first take of the medicine, or it might start later;
- severe and frequent diarrhoea, sometimes containing blood, as this may indicate a more serious condition (pseudomembranous colitis).

<u>The following side effects may also occur during the use of cefazolin containing products:</u>

Common: may affect up to 1 in 10 people
- mild gastrointestinal disturbances (loss of appetite, diarrhoea, nausea, vomiting, severe and frequent diarrhoea). These side effects usually resolve after a few days;
- injection into the muscle may cause pain at the location of the injection which may sometimes include hardening of the skin and soft tissue at the same site.

Uncommon: may affect up to 1 in 100 people
- oral thrush (thick white or cream-coloured deposits in the mouth and tongue);
- fits/convulsions in patients with kidney problems;
- swelling of a vein caused by a blood clot forming following injection into the vein (thrombophlebitis).

Rare: may affect up to 1 in 1000 people
- bacterial infection of male or female genitals with symptoms such as itching, redness, swelling and female discharge (genital candidiasis, monoliasis, vaginitis);
- increase or decrease in blood glucose concentration (hyperglycaemia or hypoglycaemia).
- reversible blood abnormalities including the reduction or increase in the number of red and white blood cells (leukopenia, granulocytopenia, neutropenia, thrombocytopenia, leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia and eosinophilia) which may cause bleeding, easy bruising and/or skin discolouration (confirmed by blood test);
- feelings of dizziness, tiredness and a general feeling of being unwell;
- sleep disorders including nightmares and being unable to sleep (insomnia);

- feelings of nervousness or anxiety, drowsiness, weakness, hot flushes, disturbed colour vision, vertigo and epileptic seizures (involuntary rapid and repeated muscle contraction and relaxation);
- chest pain, excess fluid in the lungs, shortness of breath, cough, stuffy nose (rhinitis);
- liver problems (such as transient elevation of alkaline phosphatase or transient hepatitis) with symptoms such as an increase in liver enzymes (alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (gamma GT) and lactate dehydrogenase (LDH)) and bilirubin (a product of the breakdown of blood cells) in bile or urine (diagnosed by blood test);
- kidney problems (nephrotoxicity, interstitial nephritis, undefined nephropathy, proteinuria) with symptoms such as kidney swelling and an increase of nitrogen in the body that may be diagnosed by urine tests, usually only occurring in patients taking cefazolin at the same time as other medicines that can cause kidney problems.

Very rare: may affect up to 1 in 10,000 people
- itching of the anus or genitalia (pruritus);
- blood not clotting properly which may result in increased bleeding. This may be resolved by increasing vitamin K intake and should be confirmed by blood test.

How to store Cefazolin AptaPharma

This medicine cannot be stored above 25°C. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children. The reconstituted solution should be administered immediately after preparation.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Cefazolin AptaPharma 1 g powder for solution for injection/infusion. The procedure was finalised at 14 December 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Austria, Bulgaria, Chech Republic, Croatia, Poland, Romania, Slovenia, Slovakia) concerned the generic version of cefazolin sodium 1 g.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC (generic application) and there-fore contained no new clinical or preclinical data, other than supporting literature where necessary.

The reference product is Kefzol 1 g - Trockenstechampullen powder for solution for injection/infusion by Astro-Pharma GmbH, approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Cefazolin AptaPharma 1 g powder for solution for injection/infusion from Apta Medica Internacional d.o.o.

Cefazolin AptaPharma 1 g powder for solution for injection/infusion is indicated for the treatment of the following infections caused by cefazolin-susceptible micro-organisms:
• skin and soft tissue infections
• bone and joint infections.

The product is indicated for perioperative prophylaxis as well.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

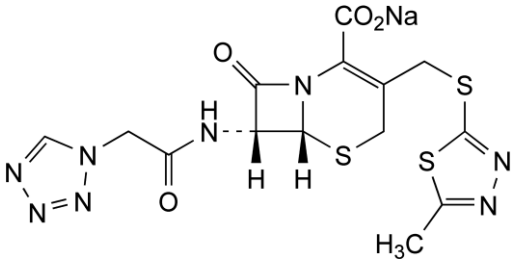
The chemical-pharmaceutical assessment report concerns the application of Cefazolin AptaPharma 1 g powder for solution for injection/infusion via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The product has been developed by ACS Dobfar S.p.A.

The reference medicinal product is Kefzol 1 g powder for solution for injection/infusion, which was the product of Astro-Pharma GmbH, Austria.

II.2 Drug substance – cefazoline sodium

Data on the quality and manufacture of the active substance were provided in the applicant's submission using CEP procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Cefazolin Sodium
Chemical name: Sodium (6R,7R)-3-[(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-8-oxo-7-[(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Structure:



The active substance is white or almost white powder, very hygroscopic. It is freely soluble in water, very slightly soluble in ethanol 96%.

The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Re-test periods and the packaging materials have been mentioned on the Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP).

Good Manufacturing Practice (GMP) compliance of the active pharmaceutical ingredient (API) manufacture is demonstrated by the Applicant.

II.3 Medicinal product

The aim was to develop a generic product of Cefazoline for injection/infusion (sterile powder corresponding to 1 g of Cefazolin) essentially similar to the one which has already been marketed in E.C. member states for over 10 years.
A satisfactory package of data on development pharmaceutics has been presented. The chosen sterilization method of the drug product is justified.
As a result of development studies product with the following appearance was obtained:

- white or almost white sterile powder.

The drug product consist of the sterile Cefazolin sodium without any excipients.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The primary packaging material of the product is glass vial type III, closed with bromobutyl rubber stopper, and sealed with aluminium caps with flip-off/polypropylene (PP) disc. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following special storage restrictions:
‘Do not store above 25°C. Keep the vials in the outer carton in order to protect from light.’

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end

of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of cefazolin are well known. As cefazolin is a widely used, well-known active substance, no further studies are required and the applicant provided none. Overview based on literature review is, thus, appropriate. The Non-clinical overview is adequate. Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

III.2 Pharmacology

All cephalosporins (β-lactam antibiotics) inhibit the bacterial cell wall production and are selective inhibitors of the peptidoglycan synthesis. The first step in the mode of action is the binding of the drug to the cell receptors (penicillin-binding proteins). After this binding the transpeptidase reaction is inhibited and this blocks the synthesis of peptidoglycan. This process results in the lysis of the bacteria.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

III.4 Toxicology

Published information on toxicological studies with cefazolin was the basis for the evaluation. No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmnetal risk assessment (ERA)

This generic application does not represent a new indication nor a significant increase in the extent of use of the substance. This application presents the same indications of use, precautions and warnings as the reference products, which are adequate to ensure environmental safety when the product is used as directed. Therefore, the product is not expected to pose a risk to the environment when is used as recommended.

III.6 Discussion onthe non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of cefazolin are well-known. As Cefazolin AptaPharma 1g powder for solution for injection/infusion is a generic product, there is no need for further excessive non-clinical studies. The non-clinical part of the application was acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application contains an adequate review of published clinical data.
The clinical pharmacology of cefazolin is well known.

IV.2 Pharmacokinetics

Bioequivalence, Biowaiver

The medicinal product 'Cefazolin AptaPharma 1 g Powder for Solution for Injection' is a pure generic, in that it contains the same drug substance, cefazolin, in the same pharmaceutical form, a sterile powder for injection, at the same strength, 1 g, as the originator brand products, such as Kefzol 1 g - Trockenstechampullen Powder for solution for injection/infusion (Astro-Pharma GmbH, Austria).
In compliance with Appendix II of the Guideline on the Investigation of Bioavailability and Bioequivalence – *CPMP/EWP/QWP/1401/98 Rev. 1, Corr* ** of 20th January 2010, bioequivalence studies were not required.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of and none are required for applications of this type. Cefazolin AptaPharma 1g powder for solution for injection/infusion.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of cefalexin.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of cefalexin.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

As the active substance has been used for decades and its safety concerns are well-known so there were no safety concerns applicable for this EU RMP based on the requirement to present only the important identified or potential risks and missing information linked to further pharmacovigilance activities or additional risk minimization measures in the EU.

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Aptapharma’s product containing cefazoline.

No additional activities are proposed.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Aptapharma’s product containing cefazoline.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.
Cefazolin AptaPharma 1g powder for solution for injection/infusion is indicated for the treatment of the following infections caused by cefazolin-susceptible micro-organisms:
• skin and soft tissue infections
• bone and joint infections.

The product is indicated for perioperative prophylaxis as well.

There were no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Cefazolin AptaPharma 1 g powder for solution for injection/infusion. The applicant and the future holder of authorisation is Apta Medica Internacional d.o.o.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was Kefzol 1 g - Trockenstechampullen Powder for solution for injection/infusion by Astro-Pharma GmbH, authorised for marketing since 1974.

The product is indicated for the treatment of the following infections caused by cefazolin-susceptible micro-organisms:
• skin and soft tissue infections
• bone and joint infections.

The product is indicated for perioperative prophylaxis as well.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Cefazolin AptaPharma 1 g powder for solution for injection/infusion from Apta Medica Internacional d.o.o.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 patient information 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. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached