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Public Assessment Report

Name of the Product:

Cefotaxim AptaPharma 1 g, 2 g powder for solution for injection and infusion

(cefotaxime)

Procedure number: HU/H/0588/001-002/DC

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

Date: 7 July 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Cefotaxim AptaPharma 1 g, 2 g powder for solution for injection and infusion. The holder of the marketing authorisation is Apta Medica Internacional d.o.o., Slovenia.

The active substance is cefotaxime. One vial contains 1.048 g or 2.096 g cefotaxime sodium (equivalent to 1 g or 2 g cefotaxime).

The product does not contain any other ingredients.

Appearance: white to pale yellow powder.

Pack size: the Cefotaxim AptaPharma 1 g powder for solution for injection/infusion is in 10 mL, the 2 g powder for solution for injection/infusion in a 20 mL uncoloured glass vials, in carton.

The active substance of this product is a cephalosporin antibiotic. It has a pronounced activity against a wide range of bacteria that cause many and sometimes serious infections in humans. It works by inhibiting the formation of the bacterial cell wall, thus preventing bacterial multiplication.

Cefotaxim AptaPharma 1 g and 3 g powder for solution for injection and infusion (further on: Cefotaxim AptaPharma) is used to treat infections caused by susceptible to cefotaxime microorganisms, such as:
- septicaemia (spread of microbes and their toxins in the blood);
- respiratory tract infections – acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, pulmonary abscess and post-operative chest infections;
- urinary tract infections – acute and chronic infections of the kidney (pyelonephritis), bladder (cystitis) and asymptomatic bacterial infections (asymptomatic bacteriuria);
- Skin and soft tissue infections;
- bone and joint infections;
- obstetric and gynecological infections;
- infections of the abdomen;
- gonorrhea (sexually transmitted disease), where penicillin therapy is inappropriate or has not produced the expected effect;
- infections of the thin membranes of the brain (meningitis).

Cefotaxim AptaPharma is also used to prevent infections before and after surgery.

What patients need to know before using Cefotaxim AptaPharma

Patients who are allergic to cefotaxime or any other cephalosporin antibiotics must not use Cefotaxim AptaPharma.

Signs of an allergic reaction include: rash, difficulty swallowing or breathing, swelling of the lips, face, throat or tongue. Patients who have previously had allergic reactions to penicillins must discuss it with their doctor as cross-sensitivity between penicillins and cephalosporins is possible.

Cefotaxim AptaPharma, diluted with lidocaine, should never be used:
- intravenously;
- in children <30 months of age;
- in patients allergic to lidocaine or other local anesthetics of the amide type;
- in patients with heart rhythm disturbances, e. g. cardiac block if there is no pacemaker;
- in patients with severe heart failure.

Warnings and precautions

Patients with he following conditions should talk to zheir doctor or nurse before using Cefotaxim AptaPharma:
- if they are allergic to any antibiotics, especially to an antibiotic called penicillin;
- if they have an allergy or suffer from bronchial asthma. The possibility of allergic reactions, in some cases very serious, cannot be excluded during treatment with this product. Therefore, before starting treatment, the doctor will perform specific skin tests to check whether the patient is allergic to the medicine;
- if they have kidney problems;
- if they are on a controlled sodium diet;
- if they have ever had severe diarrhea after taking antibiotics ("pseudomembranous colitis"). Patients having severe diarrhea should contact their doctor immediately as they may need urgent medical attention. They should not take any anti-diarrhoeal medicine without consulting the doctor.

Tell your doctor immediately if you Patients who experience any skin and/or mucous reaction (rash, blistering, scaling or skin peeling)must discuss their doctor before they continue using Cefotaxim AptaPharma. These may be signs of serious, life-threatening skin conditions (Stevens-Johnson syndrome, toxic epidermal necrolysis).

High doses of cefotaxime, particularly in patients with renal insufficiency, may cause damage to central nervous system (consciousness disturbances, movement disorders and convulsions). If such reactions occur, the doctor must be contacted immediately for advice.

As with other antibiotics, "overgrowth" of cefotaxime-resistant microorganisms, including fungi may occur with prolonged treatment. In such cases, the patient should start a specific treatment as determined by the doctor based on the patient’s condition.

Periodic blood tests should be performed during prolonged treatment (over 7-10 days), because the number of some blood cells may decrease while the number of others may increase. In some cases, this may require cessation of treatment.

It is recommended to strictly observe the injection or infusion time as there have been reports of life-threatening heart rhythm disturbances (arrhythmias) in very few patients who received cefotaxime by a rapid intravenous injection through a central venous catheter.

Other medicines and Cefotaxim AptaPharma

Patients should tell their doctor if they are taking, have recently taken or might take any other medicines.

The doctor should be consulted if taking any of the following medicines:
- aminoglycoside antibiotics – gentamicin, streptomycin, neomycin, kanamycin, amikacin or tobramycin,
- tetracycline and chloramphenicol antibiotics,
- water tablets (diuretics), e.g. furosemide,
- probenecid, a medicine used to treat gout,
- oral contraceptives.

Laboratory tests

If a patient needs to have a laboratory test while using this medicine (e.g. blood or urine tests), the doctor must be informed that the patient is currently using cefotaxime. Cefotaxime, as well as other antibiotics, may cause false positive blood sugar and urine sugar tests and Coombs' test.

Cefotaxim AptaPharma with food, drink and alcohol

No restrictions are known.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

During pregnancy, the doctor will decide whether the patient should receive cefotaxime by considering the benefit/risk ratio. Cefotaxime passes into breast milk and therefore should not be used during breast-feeding.

Cefotaxime may reduce the efficacy of oral contraceptives. Using complementary contraceptive methods is recommended during cefortaxime-therapy.

Driving and using machines
Cefotaxime may cause dizziness, which may affect the ability to drive and use machines. Those who experience this side effect, should not drive or use machines.

During treatment with high doses of the antibiotic, patients may experience consciousness disturbances, abnormal movements and convulsions. In such cases, they should not drive or use machines.

Cefotaxim AptaPharma contains sodium

Cefotaxim AptaPharma 1 g powder for solution for injection/infusion contains approximately 2.1 mmol (approximately 48 mg), the 2 g for solution for injection/infusion contains approximately 4.2 mmol (approximately 96 mg) of sodium (main component of cooking/table salt) in each 1.0 g or 2.0 g. This is equivalent to 0.024 % (0.048 %) of the recommended maximum daily dietary intake of sodium for an adult per 1.0 g (2.0 g) dose which should be taken into consideration by patients on a controlled sodium diet.

How to use Cefotaxim AptaPharma

Cefotaxim AptaPharma will be given to patients by a doctor or a nurse.

The product can be given intramuscularly or into the vein. The dose, route and frequency of administration are determined depending on the severity of the infection, the susceptibility of the bacterium and the condition of the patient.

What to do if more Cefotaxim AptaPharma was administered than it should have been?

It is unlikely that a healthcare professional will give a patient a higher dose of the medicine. In case of any doubt, the doctor should be consulted.

What to do if using Cefotaxim AptaPharma has been forgotten?

If a single dose has been missed, it should be given as soon as possible unless it is almost time for the next dose. Otherwise, the next dose should be given to the patient at the usual time.

Possible side effects

Like all medicines, Cefotaxim AptaPharma can cause side effects, although not everybody experiences them.

Side effects associated with cefotaxime use are usually rare and are generally mild and transient.

Patients must tell their doctor immediately if they experience any of the following serious side effects, as they may need urgent medical attention:

- getting an allergic reaction. Signs may include: rash, itching, fever, difficulty in breathing or wheezing, chills, swelling;
- getting blisters on the skin, mouth, eyes and genitals. These may be a sign of a severe skin disease (Stevens-Johnson syndrome or toxic epidermal necrolysis);

- having sudden involuntary muscle spasms, convulsions and loss of consciousness. This condition is called "encephalopathy" and is usually observed with high doses, especially in patients with renal insufficiency;
- feeling palpitations or skipped heart beats;
- getting severe watery diarrhoea, possibly mixed with blood and mucus ("pseudomembranous colitis").

The side effects given below are listed by frequency.

Very common (may affect more than 1 in 10 patients): when given intramuscularly, transient pain at the injection site, usually at high doses

Uncommon (may affect up to 1 in 100 patients): change in the number of blood cells (leukopenia, eosinophilia, thrombocytopenia); convulsions; diarrhoea; transient, reversible increases in liver enzymes, alkaline phosphatase and bilirubin; hypersensitivity reactions: rash, itching, urticaria, drug fever; impaired kidney function and elevated creatinine (especially with high doses or concomitant treatment with aminoglycoside antibiotics); fever; inflammation of the injection vein (phlebitis/thrombophlebitis); Jarish-Herxheimer's reaction, which is manifested by skin rash, itching, runny nose, blood and liver problems, difficulty in breathing, and joint problems.

Not known (cannot be estimated from the available data): overgrowth of non-susceptible organisms during prolonged use and serious infections; significant reduction in white blood cell counts (neutropenia and agranulocytosis), which increases the likelihood of infections; reduced red blood cell count (haemolytic anemia), which may lead to pallor or yellowing of the skin, asthenia or shortness of breath; headache, dizziness; encephalopathy; heart rhythm disturbances, usually in rapid intravenous administration; nausea; vomiting; abdominal pain, pseudomembranous colitis; hepatitis (sometimes with jaundice); severe skin diseases – Stevens-Johnson syndrome (associated with blistering of the skin, mouth, eyes and genitals), toxic epidermal necrolysis (with blistering of the skin) and erythema multiforme; kidney tissue damage (interstitial nephritis); when used intramuscularly (if the solution contains lidocaine) – general reactions typical of lidocaine; serious allergic reactions – oedema around the eyes, lips, tongue which may be life-threatening (angioedema), difficulty breathing, wheezing (bronchospasm), allergic shock.

How to store Cefotaxim AptaPharma

This medicinal product does not require any special temperature storage conditions. The vial should be kept in the outer carton in order to protect from light, and out of the sight and reach of children.

When stored, the colour of the reconstituted solution may become more intense.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Cefotaxim AptaPharma 1 g, 2 g powder for solution for injection and infusion. The procedure was finalised at 30 April 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, Croatia and Slovenia) concerned the generic version of cefotaxime sodium 1 g and 2 g powder for solution for injection and infusion (spelled Cefotaksim in Croatia).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The reference products are Claforan 1 g and 2 g powder for solution for injection/infusion marketed by Sanofi Aventis approved for more than 10 years within the European Economic Area. In case of aqueous solution of similar composition the bioequivalence to the reference products can be demonstrated without in vivo studies.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Cefotaxim AptaPharma 1 g, 2 g powder for solution for injection and infusion from Apta Medica Internacional d.o.o., Slovenia.

Cefotaxime is indicated for the treatment of patients with serious infections caused by susceptible strains microorganisms. It is very effective alone as monotherapy or in combination for empirical treatment of severe infections caused by gram-negative bacteria. These include infections of the respiratory system, especially hospital pneumonia, complicated urinary tract infections, peritonitis, complicated gynecological infections, bacterial inflammations of the skin, bones and soft tissues, Lyme disease.

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

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application for Marketing Authorisation via the Decentralised Procedure for product Cefotaxim AptaPharma 1 g and 2 g powder for solution for injection and infusion according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. a generic application).

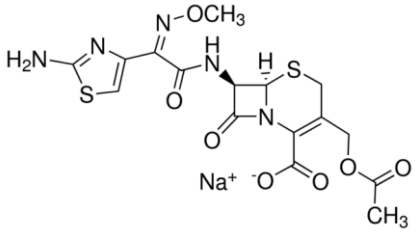
The reference medicinal product is Claforan 1 g and 2 g powder for solution for injection/infusion (Sanofi-Aventis Zrt.).

The sterile drug substance is filled. in the packaging to use it as drug product. The products contain 1 g or 2 g of the active substance cefotaxime in the form of sodium salt. The drug product is packed in clear colourless glass vials, stoppered by a bromobutyl rubber closure, capped with an aluminium cap and a plastic flip-off disk.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure in the marketing authorization dossier. The Quality Overall Summary is adequate.

I.N.N.: cefotaxime sodium
Chemical name: sodium (6R,7R)-3-[(acetyloxy)methyl]-7-[[(2Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.
Structure:



The active substance cefotaxime is an established drug substance, the sodium salt is described in the Ph. Eur.

The drug substance is freely soluble in water, sparingly soluble in methanol. It shows isomerism.

All aspects of the manufacture and control of the drug substance, cefotaxime sodium, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) CEP.

The drug substance has been specified according to the requirements of the current Ph. Eur. monograph on cefotaxime sodium with additional requirements stated on the CEPs.

Analytical procedures are performed using methods in accordance with the Ph. Eur. monograph on cefotaxime sodium and the CEPs.

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 period of the drug substance has been assigned in the CEP or the stability data are provided in the dossier.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The pharmaceutical development aimed to manufacture a stable powder for solution/infusion as a generic formulation of Reference product Claforan powder for solution for injection/infusion. The same quantity of drug substance in one vial and the same route of administration is used.

The drug product does not contain any excipients.

Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

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 International Council of Harmonisation (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 testing results of the batches demonstrate that the drug product can be manufactured in a consistently good quality.

The provided data and documents regarding the container- closure system confirm the suitability of the immediate packaging materials.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years is approved with the following storage condition: 'This medicinal product does not require any special temperature storage conditions. Keep the vial in the outer carton in order to protect from light.'

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

Cefotaxim AptaPharma 1 g and 2 g powder for solution for injection and infusion 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.

From quality points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of cefotaxime are well known. As cefotaxime is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate. The submitted overview is adequate.

III.2 Pharmacology

Cefotaxime is a semi-synthetic third generation cephalosporin for parenteral use. The mechanism of action of cefotaxime is like that of all cephalosporins. It possesses bactericidal activity inhibiting the bacterial wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins.

Cefotaxime sodium has in vitro activity against a wide range of gram-positive and gram-negative organisms. It has a high degree of stability in the presence of β-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Cefotaxime has been shown to be active against most strains of microorganisms both in vitro and in clinical infections.

III.3 Pharmacokinetics

Cefotaxime is administered intravenously or intramuscularly. There is no evidence of accumulation following administration.

Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of cefotaxime is excreted in the urine.

III.4 Toxicology

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Cefotaxim AptaPharma 1 g and 2 g powder for solution for injection and infusion are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals. The literature overview presented on non-clinical characteristics of cefotaxime is adequate.

From non-clinical aspects the product is approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cefotaxime has a well-established efficacy and safety profile and is generally well-tolerated. As it is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate. The submitted overview is adequate.

To support the application, the applicant did not carry out any clinical study including bioequivalence one.

IV.2 Pharmacokinetics

No bioequivalence study has been conducted. For both Cefotaxim AptaPharma and the reference product Claforan (Sanofi Aventis) are powders for solution, without excipients, they can be considered bioequivalent according to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/corr*.

According to literature data, after a 1000 mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 μg/mL. Doses of 500 mg and 2000 mg produce plasma concentrations of 38 and 200 μg/mL, respectively. There is no evidence of accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of cefotaxime is 21.6 l/1.73m^2 after 1 g intravenous 30-minute infusion.

Cerebrospinal fluid concentrations are lower when the meninges are not inflamed, but are between 3 and 30 μg/mL in children with meningitis. Cefotaxime usually passes the blood-brain barrier in levels above the minimum inhibitory concentration of common sensitive pathogens when the meninges are inflamed.

Concentrations (0.2-5.4 μg /mL), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most susceptible organisms are similarly attained in female reproductive organs, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and its metabolite desacetyl-cefotaxime are attained in bile.

Most of a dose of cefotaxime is excreted in the urine - about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390 mL/min and renal clearance 145 to 217 mL/min.

After intravenous administration of cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours. In neonates, the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

IV.3 Pharmacodynamics

Cefotaxime is a third-generation broad spectrum bactericidal cephalosporin antibiotic. The bactericidal properties are due to the inhibitory effect of cefotaxime on bacterial cell wall.

Resistance to cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyse cephalosporins, to the induction and/or constitutive expression of AmpC enzymes, to impermeability or to efflux pump mechanisms.

Antibacterial spectrum of cefotaxime is as follows.

Gram-positive aerobes:
- *Staphylococcus aureus* (penicillinase-producing and not producing strains),
- *Staphylococcus epidermidis*,
- *Streptococcus pyogenes* (Group A),
- *Streptococcus agalactiae* (Group B),
- *Streptococcus pneumoniae* (Streptococcus faecalis and other Group D Streptococcus strains are usually resistant!),
- Corynebacterias.

Gram-negative aerobes
- *Neisseria gonorrhoeae* (penicillinase-producing and not producing strains),
- *Neisseria meningitides,*
- some Pseudomonas strains,
- *Escherichia coli*
- Enterobacter species (some strains are resistant!),
- *Proteus mirabilis,*
- *Proteus vulgaris,*
- *Providencia rettgeri,*
- Klebsiella species,
- Citrobacter species,
- *Morganella morganii,*
- Shigella,
- Serratia species,
- *Haemophilus influenzae* (including ampicilline resistant strains).

Gram-positive anaerobes
- Peptococcus species,
- Peptostreptococcus species,
- Clostridium species (majority of *Clostridioides difficile* is resistant!),

Gram-negative anaerobes: Bacteroides species, among them some *Bacteroides fragilis* strains.

Resistant strains:
- MRSA, MRSE strains,
- Enterococcus species,
- Chlamydia species,
- Mycoplasma species,
- Majority of *Bacteroides fragilis* and *Clostridioides difficile* strains.

IV.4 Clinical efficacy

The applicant has not conducted clinical efficacy studies.

Based on published evidence in contemporary literature and the vast clinical experience with cefotaxime treatment, the conclusion can be made of its enormous significance in the therapy of severe bacterial infections. It is listed as drug of choice in the guidelines of medical associations.

IV.5 Clinical safety

The applicant has not conducted clinical safety studies. Since Cefotaxim AptaPharma and Claforan powders for solution can be considered bioequivalent, their safety profiles are the same.

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 Good Pharmacovigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

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 Risk Management Plan 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 European Union.

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Apta Medica's product containing cefotaxime. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Apta Medica's product containing cefotaxime. 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

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence (as described in section IV.2) is pivotal.

Cefotaxim AptaPharma and Claforan (Sanofi Aventis) powders for solution for injection and infusion can be considered bioequivalent.

From clinical points of view the product is approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Cefotaxim AptaPharma 1 g and 2 g powder for solution for injection and infusion, generic versions of cefotaxime. The applicant and the future holder of authorisation is Apta Medica Internacional d.o.o.

The indication is the treatment of patients with serious infections caused by susceptible strains microorganisms. Cefotaxime is very effective alone as monotherapy or in combination for empirical treatment of severe infections caused by gram-negative bacteria. These include infections of the respiratory system, especially hospital pneumonia, complicated urinary tract infections, peritonitis, complicated gynecological infections, bacterial inflammations of the skin, bones and soft tissues, Lyme disease.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Claforan 1 g and 2 g powder for solution for injection/infusion (Sanofi Aventis).

To support the application the applicant has adequately justified the absence of *in vivo* bioequivalence studies with these aqueous solutions on the basis of bioequivalence guideline (*Appendix III, CPMP/EWP/QWP/1401/98/rev 1/Corr***).

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 Cefotaxim AptaPharma 1 g and 2 g powder for solution for injection and infusion,

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