Public Assessment Report

Scientific discussion

Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion (ganciclovir sodium)

NL/H/2828/001/DC

Date: 7 July 2014

This module reflects the scientific discussion for the approval of Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion. The procedure was finalised on 13 January 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 8-10.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion from ADOH B.V.

The product is indicated for the treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infections in immunocompromised individuals. These states include acquired immunodeficiency syndrome (AIDS) or iatrogenic immunosuppression associated with transplantation of hematopoietic stem cells, bone marrow or a solid organ.
Ganciclovir is also indicated for the prevention of CMV disease, specifically in those patients receiving immunosuppressive therapy secondary to transplantation of hematopoietic stem cells, bone marrow or a solid organs.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cymevene 500 mg, powder for solution for infusion (NL License RVG 13007), which has been registered in the Netherlands by Roche Nederland B.V. since 25 October 1988.

The concerned member states (CMS) involved in this procedure were Germany and France.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ganciclovir Adoh 500 mg is a white porous cake or powder. One vial contains 546 mg ganciclovir sodium, equivalent to 500 mg ganciclovir. After reconstitution in 10 ml water for injections, 1 ml of the reconstituted solution contains 50 mg of ganciclovir.

The primary package is a 10 ml clear borosilicate (Type I) glass vial with a gray 20 mm bromobutyl silica rubber stopper and a 20 mm aluminum cap with a plastic flip-off seal.

During the manufacturing of the finished product, only water for injections and nitrogen are used as excipients. These are however not present in the finished drug product.

II.2 Drug Substance

The active substance is ganciclovir sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.), although a Ph.Eur. monograph for ganciclovir is available. The active substance is a white or almost white crystalline powder, which is freely soluble in water at high pH and less soluble at more neutral pH. Ganciclovir sodium is practically insoluble in ethanol, ethyl acetate, cyclohexane, petroleum ether, acetone and chloroform. The drug substance does not show polymorphism and has no specific optical rotation. The MAH provided full data on the manufacture, quality control and stability of the drug substance.

Manufacturing process
Ganciclovir sodium is synthesized by a 7-step process. No class I solvents or heavy metal catalysts are used. The definition of the starting materials is acceptable. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification comprises the specifications of the Ph.Eur. Monograph on ganciclovir with additional specifications for identification, residual solvents and microbial limits. The drug substance specification is acceptable. Batch analytical data demonstrating compliance with the specification have been provided for three commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six full-scale batches stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability results show that at long term and accelerated conditions all parameters comply with the proposed specification and that no significant changes or trends were observed.
Based on the above observations a re-test period of 24 months can be granted. The proposed storage condition “Store at ambient temperature, protected from oxygen, moisture, and excessive heat” is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known and the same as in the reference product. The manufacturing process chosen for Ganciclovir Adoh is an aseptic process consisting of a non-sterile bulk solution preparation followed by sterile filtration of the solution and filling of the solution into sterilized glass vials and lyophilisation. The choice of the sterilisation method has been justified.
Sterility testing is part of the product release and end of shelf-life specification. Bacterial endotoxins are taken into account as well. The provided information is regarded as sufficient.
The product contains the same amount and concentration of the same active substance, and concerns the same pharmaceutical form, a powder for concentrate for solution for infusion without the addition of excipients, which is administered intravenously. In accordance with the applicable guideline, a bioequivalence study is not required.

Manufacturing process
Ganciclovir Adoh 500 mg is manufactured by dissolution of the drug substance in water, filtration of the solution, filling of the previously sterilized vials followed by lyophilization. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients used in the manufacturing process are water for injection and nitrogen. The specifications for the excipients are in-house which have been derived from USP and Ph.Eur. monographs of these excipients. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, completeness and clarity of solution, pH, water, bacterial endotoxins, assay, sterility, particulate matter, impurities and uniformity of dosage units. The release and shelf-life limits for all tests are the same and are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for four full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 10 mL clear glass vial (type I) with a 20 mm bromobutyl rubber gray lyo stopper and 20 mm crimp cap with flip-off top. Stability results at long-term conditions comply with the specifications set. The proposed shelf-life of 36 months is justified. The product does not require any special storage condition.
Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 20-25°C.
According to the label of the reference product Cymevene, the reconstituted ganciclovir sodium solution is diluted with the following clinical diluents: 0.9% sodium chloride, 5% glucose, Ringer's injection, lactated Ringer's injection. The compatibility of the proposed product with all these diluents has been demonstrated. Chemical and physical in-use stability of the ganciclovir containing infusion solution has been demonstrated for 24 hours at 2-8°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ganciclovir Adoh 500 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to continue the ongoing stability studies for the drug substance. The results at least up to the shelf life will be provided.
- The MAH committed to continue the ongoing stability studies for the drug product. The results at least up to the proposed shelf life will be provided.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ganciclovir Adoh 500 mg is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cymevene 500 mg powder for solution for infusion, which is available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ganciclovir is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Ganciclovir Adoh 500 mg is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Indications

The indications for treatment and prevention of CMV disease have been supported by clinical studies, which were reviewed in the MAH’s clinical overview. These are largely in line with the indications approved for the Dutch reference product Cymevene 500 mg.
The MAH has committed to submit a variation in order to implement the harmonised text after finalization of the Article 30 referral for the reference product Cymevene iv, which is part of a harmonisation procedure under Article 30(2) of Directive 2001/83/EC

IV.4 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 Ganciclovir Adoh 500 mg.

Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity
	Haematopoietic cytopenias and associated infections and haemorrhages
	Male infertility
	Seizures due to interaction with imipenem-cilastatin
Important potential risks	Exposure during breastfeeding
	Exposure during pregnancy
	Potential for overdose in patients with renal impairment
	Potential interaction with drugs which are excreted through the kidneys
	Carcinogenicity
	Potential interactions with other drugs that cause myelosuppression
Important missing information	Exposure in elderly patients
	Exposure in paediatric patients

No additional risk minimisation measures are planned for any of the important identified risks, important potential risks, or missing information. Routine pharmacovigilance practice and appropriate product labeling are considered sufficient.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cymevene 500 mg. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 PL was Dutch. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. A total of 14 questions were asked in random order and the questions sufficiently addressed the key safety messages. The questions covered the following areas: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Cymevene 500 mg, powder for solution for infusion. Cymevene 500 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ganciclovir Adoh 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 January 2014.

In addition to the quality commitments listed on page 4, the following post-approval commitment has been made:

- The MAH committed to submit a variation in order to implement the harmonised text after finalization of the Article 30 referral for the reference product Cymevene iv.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Summary Public Assessment Report

Generics

Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion

(ganciclovir)

NL/H/2828/001/DC

Date: 7 July 2014

Summary Public Assessment Report

Generics

Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion

Active substance: ganciclovir

This is a summary of the public assessment report (PAR) for Ganciclovir Adoh 500 mg. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Ganciclovir Adoh.

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

What is Ganciclovir Adoh and what is it used for?
Ganciclovir Adoh 500 mg is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Cymevene 500 mg.

This medicine is an antiviral agent that is active against the cytomegalovirus (CMV).

It is used for treatment of life-threatening or sight-threatening CMV infections in patients with an impaired immune system (patients with AIDS or patients who have undergone an organ transplantation).
This medicine can also be used for prevention of CMV disease, specifically in patients who will undergo an organ transplantation and are receiving a therapy to impair their immune system.

How is this medicine used?
The medicine can only be obtained with a prescription. Based on the patient's body weight and the severity of the condition, a doctor will determine the dosage and duration of treatment.

Common dosages	CMV infection	Prevention of CMV infection
Initial dosage	5 mg per kilogram body weight every 12 hours for 14 to 21 days.	5 mg per kilogram body weight every 12 hours for 7 to 14 days.
Maintenance dosage	6 mg per kilogram body weight per day 5 days a week, or 5 mg per kilogram body weight per day 7 days a week.	6 mg per kilogram body weight per day 5 days a week, or 5 mg per kilogram body weight per day 7 days a week until 100 days after transplant.

In patients with impaired renal function, the doctor may adjust the dosage. Ganciclovir Adoh is administered by a doctor via an infusion. This infusion takes one hour.

How does this medicine work?
Ganciclovir is an inhibitor of viruses. Individuals with an impaired immune system are much more likely to get a severe viral infection than healthy individuals. An impaired immune system occurs for example in people with HIV and AIDS or after organ transplantation. Ganciclovir inhibits the growth of the virus and thus treats the cause of the infection. The virus is not killed, but remains in the body and can cause symptoms again.

How has this medicine been studied?
The company provided data from the published literature on ganciclovir. No additional studies were needed as Ganciclovir Adoh 500 mg is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Cymevene 500 mg.

What are the benefits and risks of this medicine?
Because Ganciclovir Adoh is a generic medicine, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, this medicine contains the same amount of active substance and has been shown to have comparable quality to Cymevene. Therefore, the view was that, as for Cymevene, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine 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 Ganciclovir Adoh, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about this medicine
In the Netherlands, the marketing authorisation for Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion was granted on 21 February 2014.

The full PAR for Ganciclovir Adoh can be found on the website http://mri.medagencies.org/Human. For more information about treatment with this medicine, read the package leaflet (http://mri.medagencies.org/download/NL_H_2828_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in July 2014.