CBG MEB

Public Assessment Report

Scientific discussion

Apotel 10 mg/ml, solution for infusion

(paracetamol)

NL/H/2857/001/DC

Date: 16 December 2014

This module reflects the scientific discussion for the approval of Apotel 10 mg/ml, solution for infusion. The procedure was finalised on 11 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apotel 10 mg/ml, solution for infusion from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

The product is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

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 Perfalgan 10 mg/ml solution for infusion (NL License RVG 26961) which was registered in the Netherlands by Bristol-Myers Squibb B.V. in 2002 through procedure FR/H/0197/001. This product is no longer registered in the RMS, but reference is made to the historical product which is deemed appropriate.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Apotel 10 mg/ml is a clear, colourless to slightly yellowish solution with pH 4.5 – 6.0 during shelf-life and osmolarity of approximately 290mOsmol/l.

The solution is packed in 100 ml polypropylene bags equipped with an infusion site, consisting of a polyolefin/styrene-block copolymer based tube. The tube is sealed with a chlorobutyl rubber stopper and an aluminium cap. The bags are overwrapped with aluminium foil, metalized film or with a polyethylene-based multilayer film. Each 100 ml bag solution for infusion contains 1000 mg paracetamol.

The excipients are: hydroxypropylbetadex, disodium edetate, sodium chloride, sodium dihydrogen phosphate dihydrate, (pH adjustment, E339), disodium hydrogen phosphate dihydrate (pH adjustment, E339) and water for injection.

II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Paracetamol is a white or almost white crystalline powder, which is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP, with an additional parameter for microbiological quality. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product at issue and the reference product differ with respect to the qualitative composition. The reference product uses mannitol as the solubilising agent, whereas the generic formulation contains hydroxypropylbetadex as a stabiliser. This difference was justified in terms of bioequivalence and has been evaluated from a clinical point of view.
The pH of the test product is comparable to the pH of the reference product, data on osmolarity are also similar. It was demonstrated that the excipients have no impact on the viscosity of the solution.
The sterilization method of choice is terminal sterilization; the non-standard conditions are considered acceptable. As paracetamol is known to be unstable in the presence of oxygen, measurements and controls with respect to the minimisation of residual oxygen in the solution were presented. Compatibility with the filter is demonstrated. Overall, the pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process consists of dissolving and mixing the various components, followed by filtration, filling into the final containers and sterilization. The product will be filled in a 100 ml container, the filling volume is not less than 102% of 100 ml. The overfill has been justified. Since a non standard sterilisation method is applied, full scale validation data is required. An additional full scale validation batch will be performed after registration for one of the manufacturing sites.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance-odour, pH, extractable volume, identification, assay, related substances, uniformity of dosage units, visible and subvisible particles, dissolved oxygen, relative density, osmolality, sterility and bacterial endotoxins. Release and shelf-life limits are identical, except for the pH and related substance.
The analytical methods have been adequately described and validated in line with the ICH guidance. The method for assay and related substances are stability indicating. Batch analysis data have been provided for five batches of the approved scale, one smaller and one larger batch from two different sites.

Stability of drug product
Stability data have been provided for five batches of the approved scale, one smaller and one larger batch from two different sites, packed in the commercial packaging material. The batches were stored at 25°C±2°C/40%±5% RH (24 months) and at 40°C±2°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline on semi-permeable containers.
Stability results at long term conditions do not show specific changes or trends for the parameters appearance, impurities, particulate contamination, dissolved oxygen, sterility test and bacterial endotoxins. Changes are noted in the pH, extractable volume and assay, but the results are within limits. For the newer batches only 3 months data is provided. These results show no (major) differences with the already provided results. Also at accelerated conditions no specific changes or patterns are noted up to now. Photostability studies showed that the product is sensitive to light.
Based on the stability data provided, a shelf life of 2 years has been granted. The applicable storage conditions are ‘Keep the bags in the outer carton to protect the product from light’ and ‘Do not refrigerate or freeze’.

In-use stability studies demonstrated chemical and physical in-use stability for 24 hours at 25°C without overwrapping.

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 Apotel 10 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:
- The MAH committed to provide data on an additional full scale validation batch after registration of the product from one manufacturing site.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Apotel 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 Perfalgan, which is available on the European market. Reference is made to 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

Paracetamol 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

Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours. The volume of distribution of paracetamol is approximately 1 l/kg. Paracetamol is not extensively bound to plasma proteins. It is metabolised mainly in the liver. In adults, about 60% of the drug undergoes glucuronidation and 35% undergoes sulfation. Children have limited capacity for glucuronidation and a large proportion of paracetamol is conjugated to sulfate. The metabolites of paracetamol are mainly excreted in the urine and less than 5% is eliminated unchanged. The plasma half-life is 2.7 hours.

Biowaiver

A biowaiver has been applied for in accordance with Appendix II of the Guideline on the Investigation of Bioequivalence, which states that "bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product and if the excipients included do not interact with the drug substance or otherwise affect the disposition of the drug substance."

Hydroxypropylbetadex is used as a stabilizing agent in the proposed product. Based on the literature, this excipient does not interfere with the pharmacokinetics of paracetamol. Safety in children is considered demonstrated based on literature. Extensive data on the safety in patients with renal insufficiency has been submitted. Based on the data provided it is evident that hydroxypropylbetadex is relatively safe for short-term treatment. Therefore the member states concluded that no specific warnings for patients with renal impairment regarding hydroxypropylbetadex are required in the product information.

None of the excipients included in the proposed formulation of Apotel 10 mg/ml solution for infusion affect its disposition, interfering with the absorption, drug bioavailability and/or solubility characteristics of the active substance. Therefore the member states consider that a biowaiver can be granted.

IV.3 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 Apotel.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hepatobiliary disorders (cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers) - Abnormal liver function (cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers) - Drug interaction with anticoagulants - Drug interaction with enzyme inducers - Medication errors (overdose due to confusion between mL and mg in neonates, and overdose in underweight adult patients)
Important potential risks	- N/A
Missing information	- Neonates and premature neonates, pregnant and lactating women

The MAH has laid down additional risk minimisation measures in the form of educational materials to minimise the safety concern "medication error". The MAH created a poster which contains a dosing guide strip. The dosing strip takes into account the relevant weights applicable to Apotel solution for infusion. The poster also takes into account overdosing in underweight adults. The RMP contains also information concerning a study to evaluate the effectiveness of the minimisation measures with regards to active surveillance of cases of overdose. This is in line with the innovator product (see commitments below).
In addition to the educational material the MAH included details of proposed additional risk minimisation measures which describe an active surveillance of overdose cases but also a telephone survey study.

Two commitments were noted:
- The final format of dosing strip and poster should be assessed at national level before launch of the product together with the distribution plan.
- A study protocol should be submitted in a separate procedure in which the data source, sample size, outcome measures and times are described for a telephone survey study.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Perfalgan 10 mg/ml solution for infusion. No new clinical studies were conducted. The MAH sufficiently justified that the pharmacokinetic profile of the product is similar to that this reference product. 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
Both rounds of testing showed that, for each question, all of the participants were able to find the correct information, and all of them were able to answer the questions correctly. 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

Apotel 10 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Perfalgan 10 mg/ml solution for infusion. Perfalgan is a well-known medicinal product with an established favourable efficacy and safety profile

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Apotel 10 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 June 2014.

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