PUBLIC ASSESSMENT REPORT
Scientific Discussion

PARACETAMOL MACOPHARMA 10 mg/ml, solution for infusion

Paracetamol

FR/H/472/01/MR

Applicant: MACO PHARMA

Date of the PAR: October 2011
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1. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Afssaps granted a marketing authorisation (MA) for Paracetamol Macopharma 10 mg/ml, solution for infusion from MACO PHARMA on March 18th, 2010.

*Paracetamol Macopharma 10 mg/ml, solution for injection* is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever when intravenous administration is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

This is an abridged application, submitted under Article 10.1 of Directive 2001/83/EC as essentially similar to the product Perfalgan 10 mg / ml, solution for infusion from Bristol-Myers Squibb. Perfalgan has been authorized through a Mutual Recognition Procedure (FR/H/0197/001) with France acting as RMS and involving different European countries in 2001.

No new preclinical or clinical studies were conducted, which is acceptable for this kind of application. During the procedure, no potential serious risk to public health concerns was raised.

2. QUALITY ASPECTS

2.1 Introduction

The medicinal product Paracetamol Macopharma is presented in the form of a solution for infusion containing 10 mg/ml of the drug substance paracetamol. The excipients are sodium acetate trihydrate, glacial acetic acid, sodium hydroxide and water for injection. The medicinal product Paracetamol Macopharma 10 mg/ml, solution for infusion is packed in 50ml or 100ml flexible polyolefin bag.

2.2 Drug substance

Paracetamol has a monograph in the Ph.Eur. and the manufacturers have been granted Certificates of Suitability. Paracetamol is in the form of colourless crystals or white crystalline powder; it is practically odourless with bitter taste; sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

The active substance specifications include relevant tests and the limits for impurities/degradation products have been justified. Stability studies under ICH conditions have been conducted by both manufacturers and the data provided are sufficient to confirm the retest period.
2.3 Medicinal product

The medicinal product Paracetamol Macopharma 10 mg/ml, solution for infusion is formulated with excipients described in the current Ph Eur. No excipient of human or animal origin are used in the drug product.

The development is sufficiently described in accordance with the relevant European guidelines. Comparative impurities profiles of the generic product and the reference product support the essentially similar character. The manufacturing process has been sufficiently described. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 2 years in the overwrap with no special storage precautions. After dilution in Glucose 5% or NaCl 0.9% solution, the physico-chemical stability of the solution has been demonstrated during 2 hours. The stability of the product without overwrap has been demonstrated during 24 hours.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well known. However, two main impurities are present in the final product and are due to a degradation product from paracetamol: 4-aminophenol and paracetamol dimer, whatever the type of container used.

Both impurities, paracetamol dimer and 4-aminophenol, were investigated from a toxicological point of view concerning their genotoxicity.

Paracetamol solution spiked with 0.29% of paracetamol dimer impurity was tested for mutagenic properties (Ames test) over 5 Salmonella typhimurium strains (TA 1535, TA 1537, TA 98, TA 100 and TA102) with and without metabolic activation. It was found that a positive response was given in TA 98. Moreover, paracetamol dimer, tested on its own over the same 5 strains, has shown increase of revertants in TA 1537, TA 98 (with and without metabolic activation) and TA 100 (without metabolic activation). Therefore, it can be concluded that paracetamol dimer holds a mutagenic activity in the Ames test.

However, results on in vitro micronucleus test in L 5178 Y cells with and without metabolic activation have not demonstrated a positive signal; therefore in vivo studies were necessary.

In vivo bone marrow micronucleus and liver comet assay in the mouse have not shown any genotoxic activity in both tests.

Thus, from the applicant’s arguments, although paracetamol dimer is genotoxic in vitro however it does not exhibit any genotoxicity in vivo.

Therefore a limit in paracetamol dimer < 0.1 % is accepted.
4-aminophenol (PAP) limit has been discussed with the applicant during the French marketing authorisation process. It was concluded that the acceptable limit would be set at 500 ppm. Moreover, the laboratory has made a commitment towards the French authorities that the level of PAP in the final product will be lower down as much as possible in the incoming months. Indeed, for paracetamol solution the requirements in terms of limit in PAP is less restricted than paracetamol tablets because of stability during the sterilisation process (degradation occurs) and also the frequency of administration of paracetamol solution is by far lowest compared to paracetamol tablets. Therefore, the ALARP concept should be used with a limit in PAP < 0.05%.

4. CLINICAL ASPECTS

4.1 Introduction

No formal clinical assessment was performed since paracetamol containing medicinal products have been marketed in many countries for many years and no new data was submitted. The sought indications are also in line with that for the other paracetamol solution for infusion already available in several European countries.

The mechanism of action of paracetamol is not entirely known but it is generally accepted that paracetamol presents both peripheral and central activities.

4.2 Discussion on the clinical aspects

Clinical efficacy

No new data regarding efficacy have been provided.

Clinical safety

- Patient exposure

At the time of the MRP, PARACETAMOL MACOPHARMA was never marketed, no data are provided.

- Post marketing experience

PARACETAMOL MACOPHARMA was never marketed, no data are provided.

Nevertheless, as the marketing authorisation application for PARACETAMOL MACOPHARMA is a generic application, some post marketing data should be considered:

Post marketing data from the reference product PERFALGAN 10 mg/ml, solution for infusion, which was first registered in France in June 2001 and was marketed in June 2002 and then registered in Members States through a mutual recognition procedure with France acting as reference member state, in November 2001 and marketed in EU and additional data from generics.

- A safety review has been performed by France (RMS) for the reference product in December 2009 (see Safety in special population/Paediatric population) and for generics in June 2008 and updated up to April 2010, following the reports of non serious cases of injection site pain (AE unlisted in the SmPC) which were reported in France.

Since the nature and contents of container of PARACETAMOL MACOPHARMA are the same as some generics i.e. bags (100 ml and 50 ml) the same risk of non serious cases of injection site pain may be expected.

Then the Applicant is requested to strictly monitor this adverse event.

- Safety in special populations: Paediatric population
The MAH did not provide any data. France performed a safety review for the reference product in December 2009, following the reports of paracetamol overdose which had been reported in the paediatric population: children aged from 1 day to 1 year accidentally received a dose 10 times greater than the dose prescribed. Up to 31st December 2009, 22 international cases of paracetamol overdose had been reported in children aged from 1 day to 1 year who accidentally received a dose 10 times greater than the dose prescribed. The origin of this error is the confusion between milligrams (mg) and millilitres (ml) resulting in the administration of a dose 10 times greater than the dose prescribed.

Since the strength of PARACETAMOL MACOPHARMA is the same as the strength of the reference product i.e. 10mg/ml and since bags of 50 ml are used to treat newborns, infants and children weighing less than 10 kg with the same posology of 7, 5 mg/kg per administration, i.e. 0, 75 ml solution per kg up to four times a day (and children weighing from 10 to 33 kg with a posology of 15 mg/kg), the same risk of overdose in this population is expected. In order to prevent this risk the Applicant has been requested to submit a RMP including an adapted labelling to prevent this risk, a DHCP to HCP in order to warn them of this risk, a poster dedicated to the paediatric wards in hospitals and to commit itself to developing a new form.

- Conclusions

Further to the safety review performed by France in December 2009 for cases of paracetamol overdose with the reference product in children aged from 1 day to 1 year and further to the safety review performed by the RMS in June 2008, which have been completed in April 2010, for cases of pain and burning sensation at the injection site with generics, the Applicant was requested to submit an EU RISK MANAGEMENT PLAN; the documents of risk minimisation (DHPC to HCP, poster dedicated to the paediatric wards in hospitals, development of a new presentation for children weighing up to 10 kg: vial of 10ml) are provided to the Member states.

4.3 Pharmacokinetics

The proposed medicinal product is a solution for infusion. Therefore the submission of a bioequivalence study is not applicable according to chapter 5.1.2 of the “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98).

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Paracetamol Macopharma 10 mg/ml, solution for infusion is demonstrated.

The clinical documentation provided was considered adequate.

The SPC, Package Leaflet (PL) and Labelling are in the agreed template.

Comments from CMSs have been received and taken into account. Finally, agreement between Member States was reached during procedure. There was no further discussion at the CMDh.

The mutual recognition procedure for Paracetamol Macopharma 10 mg/ml, solution for infusion was successfully finalised on November 8th, 2010.

The following post-approval commitments were made during the procedure:

Quality:
A variation will be filed, within 2 years following the granting of the MA in France, to tighten the 4-aminophenol specification.
**Risk Management Plan:**
Risk of paracetamol overdose in children aged from 1 day to 1 year by confusion between mg and ml:

1. The Applicant intends to disseminate the approved DHCP letter(s) as soon as Paracetamol Macopharma is marketed in each Member State.
2. The Applicant committed itself to ask for approval from each relevant national competent authority or organisations before dissemination of a poster or any other educational material about the correspondence between infant weight/volume to be infused per time.
3. The Applicant will develop a new paediatric specific presentation, namely a 10 ml presentation.
4. In case of significant signal detection regarding this safety concern, the Applicant committed itself to warn competent authorities and to assess if further risk minimisation actions are needed.

**Injection site reaction:**
The applicant committed to strictly monitor this adverse event in the frame of the routine pharmacovigilance program, to warn the competent authorities if relevant and to implement a risk minimisation plan if necessary.

**Pharmacovigilance:**
Should the number of ADR become important Maco Pharma commits itself to implement the use of a validated commercial safety database allowing electronic recording of cases, signal detection and submission