PUBLIC ASSESSMENT REPORT
Scientific Discussion

Ketoprofen MacoPharma
Ketoprofen MacoSol
100 mg, solution for infusion
ketoprofen

FR/H/469-470/01/DC

Applicant: Maco Pharma

Date of the PAR: October 2011
1. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Decentralised Procedures for Ketoprofen MacoPharma 100 mg, solution for infusion and its duplicate Ketoprofen Macosol 100 mg, solution for infusion were approved on 8th April 2011.

The applicant MacoPharma has submitted the application dossier for its products via a Decentralised Procedure with France acting as the Reference Member State (RMS) and Luxemburg as Concerned Member State (CMS).

Ketoprofen MacoPharma 100 mg, solution for infusion and its duplicate Ketoprofen Macosol 100 mg, solution for infusion contain ketoprofen which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (also known as NSAIDs), which relieve pain and reduce inflammation.

These prescription only medicines are indicated for adult patients aged 15 years and over in the treatment of post operative pain and the treatment of acute renal colic.

A comprehensive description of the indications and doses is given in the Summary of Product Characteristics (SPC).

The applicant MacoPharma has developed a ready-to-use parenteral preparation for ketoprofen. This medicine has been developed as a generic version of a reference product (Profenid® 100mg, powder for solution for injection (i.v.) in vial) but with a different pharmaceutical form.

These applications were therefore submitted according to Article 10(3) “hybrid” of Directive 2001/83/EC, which allows an abridged dossier for this kind of marketing authorisation. Regarding non-clinical and clinical data, the applicant has therefore undertaken a review of the available literature data in respect of ketoprofen which was first authorised in the European Union in the 1970’s.

As the pharmaceutical form and composition are different, the applicant performed a study to compare the physico-chemical properties and the impurity profile of the reference product Profenid® 100mg, powder for solution for injection (i.v.) in vial and Ketoprofen MacoPharma 1mg/ml, solution for infusion.

A study was also conducted in rabbits to evaluate the local tolerance of Ketoprofen MacoPharma 1mg/ml, solution for infusion in the new ready-to-use formulation proposed for marketing compared to the one of the reference product Profenid® 100mg, powder for solution for injection (i.v.) in vial.

A Risk Management Plan (RMP) was not submitted and one is not required for this application.

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance together with the necessary means for notification of any adverse reaction suspected of occurring.

During the procedure, no new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ketoprofen MacoPharma 100mg, solution for infusion and its duplicate Ketoprofen Macosol 100mg, solution for infusion outweigh the risks; hence a marketing authorisation has been granted.
2. QUALITY ASPECTS

2.1 Introduction

The medicinal product is a 100 mg/100ml ketoprofen, aqueous and buffered solution for infusion, packed in a 100 ml polyolefin flexible container overwrapped in an aluminium thermosealed composite bag.

2.2 Drug substance

Drug substance is ketoprofen, a well known molecule described in the Eur. Ph. It is a crystalline powder, practically insoluble in water. The drug substance manufacturers hold a CEP issued by EDQM. The drug product manufacturer controls quality of drug substance by specifications in line with the Eur. Ph. monograph. The analytical methods applied are suitably described and validated. Each CEP specifies a retest period for each drug substance manufacturer.

2.3 Medicinal product

The drug product was developed as a simple formulation allowing having a ready to use 100 mg ketoprofen I.V. injectable solution. All excipients used comply with the current edition of Eur. Ph. The manufacturing process consists in the preparation of an active bulk solution followed by a filtration, filling of bags, overwrapping and steam sterilisation. Validation of the process has been done at pilot scale. Specifications for drug product are appropriate for the pharmaceutical form Parenteral Solution for Infusion. Stability studies under ICH conditions have been performed. The data provided support the shelf life claimed in the SPC, 12 months stored protected from light. An in-use study performed under simulated hospital lighting conditions concluded that the product is stable for 2.5 hours when the bag is maintained out of the overwrapping. However, it is recommended to open the overwrapping immediately before use.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and referred to a product approved based on a full application with regard to preclinical data, no further data have been submitted in the dossier or were considered necessary.

The applicant has undertaken a review of the available literature data in respect of ketoprofen, well-known and widely used active substance. The dossier is limited to the Non-clinical Overview based on some major bibliographic references with the exception of a local tolerance study performed in rabbits. Conclusion furnished on this particular study that Ketoprofen Macopharma 100mg, solution for infusion and its duplicate Ketoprofen Macosol 100mg, solution for infusion administered by intravenous route did not induce any clinical sign and any local intolerability in rabbits was acceptable.

4. CLINICAL ASPECTS

4.1 Introduction

Ketoprofen is a well-known non selective non-steroidal anti-inflammatory drug (NSAID) of the propionic acid derivative group. Ketoprofen, like other non selective NSAIDs, inhibits the cyclooxygenase (Cox-1 and Cox-2) and blocks the prostaglandin synthesis.
Efficacy and tolerability of ketoprofen are established: ketoprofen has analgesic, anti-inflammatory and antipyretic activities and is widely used for conditions such as pain and mild inflammation in rheumatic disease and other musculoskeletal disorders. Ketoprofen has been used in rheumatology for 35 years as an antalgic at doses up to 300 mg/day.

The content of the SPC for Ketoprofen MacPharma 100mg, solution for infusion and its duplicate Ketoprofen Macsol 100mg, solution for infusion is in accordance with that accepted for the reference product Profenid® 100mg, powder for solution for injection (i.v.) in vial marketed by Sanofi Aventis France. The SPC is also in agreement with the European requirement for medicinal containing NSAIDs products.

4.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy and safety data, no new clinical studies have been performed with Ketoprofen Macopharma / Macsol 100 mg, solution for infusion. The dossier was limited to the Clinical Overview based on major bibliographic references which synthesised well-known information on clinical pharmacology, efficacy and safety of ketoprofen. For efficacy, only the parenteral use of ketoprofen for the proposed indications of post operative pain and acute renal colic has been considered in detail by the applicant. This overview on the clinical pharmacology, efficacy and safety was considered adequate.

4.3 Pharmacokinetics

For the present product, which has been developed as a generic of Profenid® 100mg, powder for solution for injection (i.v.) in vial, no bioequivalence study has been undertaken as the conditions for a biowaiver, as outlined in the Note for Guidance on the investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, have been fulfilled.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ketoprofen MacoPharma 100mg, solution for infusion and its duplicate Ketoprofen Macosol 100mg, solution for infusion are generic forms of Profenid® 100mg powder for solution for injection (i.v.) in vial but in a different pharmaceutical form, a “ready-to-use” formulation. Profenid® 100mg powder for solution for injection (i.v.) in vial is a well-known medicinal product with an established favourable efficacy and safety profile. Satisfactory chemical-pharmaceutical documentation has been provided for Ketoprofen Macopharma 100mg, solution for infusion and its duplicate Ketoprofen Macosol 100mg, solution for infusion, ensuring consistent and sufficient quality of active substance and the products. The overview on non clinical and clinical data was adequate and no new non-clinical or clinical safety concerns have been identified. Based on a non clinical study performed in rabbits, local tolerance of the new “ready-to-use” formulation appears acceptable. Extensive clinical experience with ketoprofen is considered to have demonstrated the therapeutic value of the compound, in particular in the treatment of post operative pain and the treatment of acute renal colic.

The benefit / risk ratio was therefore considered positive for Ketoprofen MacoPharma 100mg, solution for infusion and its duplicate Ketoprofen Macosol 100mg, solution for infusion. The Member State involved in the procedure recognised the French assessment of the marketing authorisation without commentaries and no discussion took place in the CMDh.