14 December 2023
EMA/586586/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ibuprofen Gen.Orph

International non-proprietary name: Ibuprofen

Procedure No. EMEA/H/C/006129/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

AR: Assessment report

AS: active substance

CEP: Certificate of Suitability of the European Pharmacopoeia

CoA: Certificate of analysis

CRS: Chemical reference substance (official standard)

ERA: Environmental risk assessment

FP: finished product

F_{pen}: Penetration factor

GC: Gas chromatography

GMP: Good manufacturing practice

HPLC: High performance liquid chromatography

HPLC-DAD: High performance liquid chromatography with diode array detector

ICH: International Conference on Harmonisation

IPC: In-process control

LOD: Limit of detection

LOQ: Limit of quantification

LoQ: List of questions

MAH: Marketing authorisation holder

ND: Not detected

NLT: Not less than

NMT: Not more than

PDE: Permitted daily exposure

PEC : Predicted environmental concentration

Ph. Eur.: European Pharmacopoeia

QP: Qualified person

RH: Relative humidity

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gen.Orph submitted on 9 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Ibuprofen Gen.Orph, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2022.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Pedea, 5 mg/ml, Solution for injection
- Marketing authorisation holder: Recordati Rare Diseases
- Date of authorisation: 29-07-2004
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/04/284/001

Medicinal product authorised in the Union where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Pedea, 5 mg/ml, Solution for injection
- Marketing authorisation holder: Recordati Rare Diseases
- Date of authorisation: 29-07-2004
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/04/284/001

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Simona Badoi

The application was received by the EMA on	9 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 July 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	21 August 2023
The PRAC Rapporteur circulated the PRAC Rapporteur Updated Assessment Report on the applicant's responses to the List of Questions to all PRAC members on	28 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint	7 September 2023

Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	2 November 2023
The CHMP Rapporteur circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 November 2023
The CHMP Rapporteur circulated the CHMP Rapporteurs Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 December 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ibuprofen Gen.Orph on	14 December 2023

2. Scientific discussion

2.1. Introduction

The product Ibuprofen Gen.Orph 5 mg/mL solution for injection has been developed by Gen.Orph, France as a generic to the innovator's product Pedea 5 mg/mL solution for injection, Recordati Rare Diseases, which was first approved in the European Union on 28 July 2004 via centralised procedure (EU/1/04/284/001). The reference product Pedea was originally designated an orphan medicinal product; the orphan designation was subsequently withdrawn in August 2014.

The application is a generic of a centrally authorised medicinal product and the eligibility under automatic access for substances already authorised via the Centralised Procedure – Article 3(3) - Generic Medicinal Product of Regulation (EC) No 726/2004 was confirmed in May 2022.

The active substance of this product is ibuprofen. Pharmacotherapeutic group: other cardiac preparations, ATC code: C01EB16.

The proposed therapeutic indication is similar to the approved indication for Pedea and is as follows:

Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.

Since this is an abridged application claiming essential similarity to the reference product, no new clinical studies have been undertaken. The applicant has provided a clinical overview based on published clinical data, where clinical pharmacology, efficacy and safety of ibuprofen were discussed. The active substance of Ibuprofen Gen.Orph is not considered a new active substance. Clinical pharmacodynamic, pharmacokinetic, efficacy and safety profiles of ibuprofen are well known. The overview is based on 86 publications from 1976 until 2022.

2.2. Quality aspects

2.2.1. Introduction

The finished product Ibuprofen Gen.Orph is presented as solution for injection containing 5 mg/mL ibuprofen as active substance.

Other ingredients are: trometamol, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

The product is available in a colourless type 1 glass ampoule as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of Ibuprofen is (2RS)-2-[4-(2-methylpropyl)phenyl] propanoic acid corresponding to the molecular formula $C_{13}H_{18}O_2$. It has a relative molecular mass of 206.3 g/mol and the following structure:

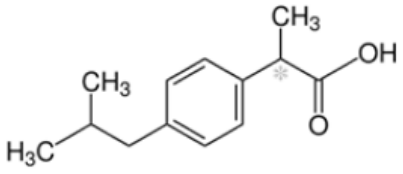

Figure 1: Active substance structure

The active substance (AS) is a white or almost white, crystalline powder or colourless crystals, practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen has one asymmetric centre, as indicated in the structure above. The compound exists as a racemic mixture.

As there is a monograph of ibuprofen in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for ibuprofen which has been provided within the current Marketing Authorisation Application.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is subjected to a CEP. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability for the source of active substance.

The active substance is packaged in lock-rim fibre *drums* which complies with EC 10/2011 as amended.

2.2.2.3. Specifications

The active substance specification includes tests and limits for: appearance (visual), identification (melting point, IR), appearance of solution (visual), optical rotation (Ph. Eur.), related substances

(HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (potentiometry) in accordance with the Ph. Eur. monograph. In addition, the CEP includes tests for residual solvents, total phosphorus. An additional test for bacterial endotoxins in the AS is performed by the finished product (FP) manufacturer, which have been described and validated.

The control tests comply with the specifications and test methods of the Ph. Eur. monograph.

The applicant has presented certificates of analysis from both the AS and the FP manufacturer, corresponding to the same three batches which were used in the manufacture of finished product. All batch results obtained were well within the applied limits.

2.2.2.4. Stability

According to the CEP, a 5year retest period is established for ibuprofen if stored in a lock-rim fibre drum.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Ibuprofen Gen.Orph 5 mg/mL solution for injection is a clear, colourless to slightly yellow solution, with a pH between 7.5 to 8.5 and an osmolality between 280-320 mOsm/kg, packed in colourless borosilicate (type I) glass ampoule with a capacity volume of 2 mL, intended for intravenous administration.

The finished product has been developed to be a generic equivalent to the reference medicinal product Pedea 5 mg/mL, solution for injection in ampoule. Consequently, the objective was to prepare a solution for injection being essentially similar to the reference medicinal product, using the same quantitative and qualitative composition.

The composition and the amount of all components as well as their functions and a reference to their quality standards have been included. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. and in section 2.1.1 of this report.

As the composition of the product is identical to the composition of the reference product, no compatibility studies between the AS and the excipients have been performed. Due to the poor solubility of ibuprofen in water in the acidic pH-range, the solution was adjusted to achieve a good solubility using sodium hydroxide and hydrochloric acid as pH adjusters. The solubility was additionally improved by the addition of a small amount of trometamol. Finally, sodium chloride is added to adjust the tonicity of the solution and to avoid irritation.

To justify the pH of the final solution, a forced degradation study using a pH range from 4 to 10 was performed. Analysis was performed after 48 hours of storage at 25°C. The results of the appearance of the solution, the ibuprofen content and of the levels of impurities have shown that ibuprofen in solution is stable at alkaline pH (pH 8 was chosen) and at pH equal to or less than 7 is not soluble and precipitates.

A comparative study between three industrial-scale batches of FP with 2 batches of reference product (of appropriate ages) demonstrated that they have the same physico-chemical characteristics.

The conditions of manufacturing process including the justification of the sterilisation process were studied and a terminal heat sterilisation according to a ICH cycle was performed by the finished product manufacturer.

Three industrial batches of final formulation were prepared according to this manufacturing process. The critical phases of the manufacturing process are preparation, filling and sterilisation all of which guarantee the stability and sterility of the finished product. The choice of the sterilisation method was justified by results of suitability studies performed for terminal sterilisation via autoclaving.

A bioequivalence study for Ibuprofen Gen.Orph 5mg/mL, solution for injection is not required because the pharmaceutical form is solution for injection for intravenous administration.

In-use stability was carried out. The aim was to control the compatibility of Ibuprofen Gen.Orph 5 mg/mL, solution for injection after dilution in two solutions for infusion as described in the SmPC of the reference product. The finished product should generally be administered as is but it can be diluted in 0.9% sodium chloride (NaCl) or 5% glucose packed in PVC-free bag. The incompatibilities stated in the SmPC were satisfactorily discussed.

Since the product is intended for parenteral use, the finished product in ampoules is sterile and meets the usual Pharmacopoeia requirements for sterility, bacterial endotoxins and particulate contamination.

The container is a one-point cut (OPC) ampoule with neck constriction, classically used for immediate packaging of parenteral solutions. The glass is transparent in the visible spectrum, thereby allowing the contents to be inspected visually. Glass type I comply with the Ph. Eur. monograph (3.2.1.).

Stability data presented in section 3.2.P.8 of this application confirm the suitability of the packaging to protect the product from ingress of microorganisms without having a detrimental effect on product quality.

2.2.3.1. Manufacture of the product and process controls

Ibuprofen Gen.Orph 5 mg/mL, solution for injection is manufactured, by HAUPT PHARMA LIVRON, 1 rue Comte de Sinard, 26250 Livron sur Drôme, FRANCE.

The choice of the manufacturing process of Ibuprofen Gen.Orph 5 mg/mL for injection is considered to be standard for this kind of pharmaceutical form.

The main steps of the manufacturing process are as follow: preparation of the ibuprofen injectable solution, filtration of the bulk solution through 0.22 µm PVDF filter, filling and sealing of the ampoule, heat sterilisation. This is considered a standard manufacturing process.

A narrative description of the manufacturing process of FP is provided in the dossier in sufficient detail. The in-process controls (IPCs) are adequate for this pharmaceutical form.

The industrial batch size of Ibuprofen Gen.Orph 5 mg/mL solution for injection has been clearly stated.

Process validation data was presented for three industrial batches covering all salient aspects of the manufacturing process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this standard process.

2.2.3.2. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), identification (HPLC-DAD, HPLC), pH (Ph. Eur.), osmolality (Ph. Eur.),

extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), visible particulate matter (Ph. Eur.), assay (HPLC), related substances (HPLC) and microbiological tests (Ph. Eur.).

The specifications comply with the relevant Ph. Eur. and ICH guideline requirements. Finished product specifications are identical at release and at shelf life.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. Batch analysis data on 3 batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three industrial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.3. Stability of the product

Stability data from three industrial batches of finished product stored for up to 12 months under long term conditions (25°C / 60% RH) and 6 months under accelerated conditions (40°C / 75% RH) were provided. Stability program was established based on ICH Guidelines regarding different conditions of temperature and relative humidity and testing frequency. The batches of FP are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Analytical procedures used were described and validated in 3.2.P.5 sections. No trends were observed on result presented after 12 months at long term and 6 months at accelerated conditions:
- Appearance, pH and particulate contamination of the three batches are stable and compliant with the specifications,
- Ibuprofen content is stable,
- Identified, unidentified and total impurities contents are not detected.
- The finished product remains sterile and endotoxins free.

A photostability study was conducted as per ICH guideline Q1B and results were presented and assessed in the development part. No degradation of the active substance in the finished product was induced by light and no other changes in the characteristics of the solution were observed. Thus, it is concluded that the product is not sensitive to light.

In-use stability study after dilution to 0.028 mg/ml has been performed when stored at room temperature for 48 h with sodium chloride 0.9% and glucose 5% in PVC-free bag of 500 ml. All

parameters tested complied with the specifications. Physicochemical compatibility for all diluents stated in the SmPC has been proven.

The applicant commits to continue the on-going studies following the protocol described. The applicant commits to add a minimum of one production batch annually to the long-term stability program if batches are manufactured.

Based on submitted stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.2.3.4. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The chemical-pharmaceutical documentation (Module 3) and Quality Overall Summary in relation to Ibuprofen Gen.Orph 5 mg/mL solution for injection are currently of sufficient quality in view of the present European regulatory requirements.

One source of active substance is proposed and CEP procedure is used. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability for the source of active substance. Ibuprofen is a well-known substance with monograph in the Ph. Eur. (0721). The control of active substance by the finished product manufacturer was provided and is acceptable.

The formulation is based on the reference medicinal product Pedea 5 mg/mL solution for injection. For the test product the same qualitative and quantitative composition is used.

The manufacturing process consists of bulk solution preparation, filtration, filling and sealing and sterilisation in ampoule. Detailed information on the description of the manufacturing process were provided. Process validation data results confirm reproducibility of the manufacturing process.

The container closure system is a 2 ml one point cut (OPC) ampoule made of colourless type I glass.

The proposed shelf-life of 24 months and storage conditions are acceptable. The proposed storage conditions and stability of diluted product are also acceptable.

Overall, information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Ibuprofen Gen.Orph manufactured by Gen.Orph is considered unlikely to result in any significant increase in the combined sales volumes for all ibuprofen containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The applicant has not performed non-clinical studies. Non-clinical data are submitted from published literature data. This is reasonable and acceptable since ibuprofen is a well-known active substance. Grounds for not providing new non-clinical data are adequately justified. The non-clinical overview is considered acceptable based on the established pharmacological, pharmacokinetic and toxicological profile and the experience from therapeutic use of the active substance.

The applicant did not present the calculation of the Predicted Environmental Concentration (PEC) as part of Phase I – estimation of exposure. However, at the time of orphan designation, patent ductus arteriosus affected approximately 2.13 in 10,000 people in the European Union (EU). This was equivalent to a total of around 81,000 people and is below the ceiling for orphan designation, which is 5 people in 10,000 (Public summary of opinion on orphan designation, Ibuprofen for the treatment of patent ductus arteriosus, 9 February 2015 EMA/COMP/158/2004 Rev.1 Committee for Orphan Medicinal Products). Moreover, according to Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1, question 4), for orphan drug submissions, F_{pen} can be refined based on the prevalence on which the medicinal orphan drug designation, as adopted by the Committee for Orphan Medicinal Product (COMP), was based. In this case, $PEC_{SURFACEWATER}$ value would be below the action limit of 0.01 µg/l.

Considering the same indication and patient population of Ibuprofen Gen.Orph 5 mg/mL solution for injection as the originator product and taking into account the small quantity used in this indication compared to the large quantity of ibuprofen used in other non-orphan indications, it is assumed that the use of the proposed medicinal product will not lead to overall increase of the environmental exposure and a risk for the environment is therefore not anticipated for ibuprofen.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Ibuprofen Gen.Orph was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a solution for injection containing ibuprofen.

No bioequivalence study has been conducted and none is required in line with the Appendix II of the *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)* since Ibuprofen Gen.Orph is a parenteral medicinal product with the same qualitative and quantitative composition in active substance and excipients as the reference product Pedea 5 mg/mL solution for injection, has the same pharmaceutical form as the reference product, is administered by a short intravenous infusion and the excipients do not interact with the drug substance and do not affect the disposition of the drug substance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of ibuprofen based on published literature. The active substance of Ibuprofen Gen.Orph is not considered a new active substance. Clinical pharmacodynamic, pharmacokinetic, efficacy and safety profiles of ibuprofen are well known. The overview is based on 86 publications from 1976 until 2022. An overview based on literature review is considered appropriate. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

This is a generic centralised application for a medicinal product supplied as a solution for injection in glass vials for single use.

No bioequivalence study was conducted and none is required according to the Appendix II of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1): "Bioequivalence studies are generally not required if the test product is to be administered as aqueous intravenous solution containing the same active substance as the currently approved product".

A biowaiver has been requested since the proposed generic medicinal product, which will be administered as an aqueous intravenous solution has an identical qualitative and quantitative composition in active substance compared to the approved reference medicinal product, Pedea 5 mg/mL solution for injection (Recordati, Rare Diseases, France), the same pharmaceutical form and route of administration. In addition, the test product contains the same excipients as the reference product and the excipients are not known to interact with the drug substance or to otherwise affect the disposition of the drug substance. That is acceptable from a pharmacokinetic point of view.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Since the product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product no bioequivalence studies have been conducted and none are required under the provisions of the Note for Guidance on the investigation of Bioequivalence and Bioavailability (CPMP/EWP/QWP/1401/98/Rev. 1): "*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*".

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

This is a generic centralised application for a medicinal product supplied as a solution for infusion in glass vials for single use.

No bioequivalence study has been submitted and none are generally required since the medicinal product is to be administered as an aqueous solution for injection for intravenous use containing the same active substance in the same concentrations as the currently authorised originator product.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 Appendix II) no bioequivalence studies are required for intravenously administered aqueous solutions if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A biowaiver has been requested since the proposed medicinal product has an identical qualitative and quantitative composition in the active substance and excipients compared to the approved reference medicinal product Pedea 5 mg/mL and the same pharmaceutical form and route of administration as an aqueous solution for injection for short intravenous infusion. That is acceptable from a pharmacokinetic point of view.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

A Clinical Overview based on published data was submitted and this is considered adequate.

2.4.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Ibuprofen Gen.Orph was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk Management Plan

2.5.1. Safety concerns

None.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to IBUGO 5 mg/mL Solution for Injection. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of ibuprofen 5 mg/mL solution for injection. The reference product Pedea 5 mg/mL solution for injection is indicated for the treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A biowaiver has been requested since the proposed medicinal product has an identical qualitative and quantitative composition in the active substance and excipients compared to the approved reference medicinal product Pedea and the same pharmaceutical form and route of administration as an aqueous solution for injection for short intravenous infusion. This is acceptable from a pharmacokinetic point of view.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

The overall benefit /risk balance of Ibuprofen Gen.Orph 5 mg/mL solution for injection is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ibuprofen Gen.Orph is favourable in the following indication:

Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.