Public Assessment Report

Scientific discussion

Paracetamol/Ibuprofen Reclinmed
Paracetamol/ibuprofen

National procedure

Date: 02.09.2024

This module reflects the scientific discussion for the approval of Paracetamol/Ibuprofen Reclinmed. The procedure was finalised at 14.06.2024. 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, State Institute for Drug Control, Slovakia, have granted a marketing authorisation for Paracetamol/Ibuprofen Reclinmed, 25 mg/ml + 20 mg/ml, oral suspension from Reclinmed s.r.o., Praha, Czech Republic. The product is indicated for the short-term symptomatic treatment of acute moderate pain in adults and adolescents over 12 years of age. A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a well-established use application of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The dosage form of the drug product is an oral suspension containing 25 mg of paracetamol per 1 ml and 20 mg of ibuprofen per 1 ml as active substances. The active substances are of pharmacopoeial quality. Quality overall summary and CV of the quality expert have been provided. Paracetamol 25 mg/ml + Ibuprofen 20 mg/ml, oral suspension is packed in amber glass type III bottles with plastic childproof caps. The approved pack sizes are 100 ml and 200 ml.

II.2 Drug Substance

The active substances are paracetamol and ibuprofen. The chemical name for paracetamol is N-(4-Hydroxyphenyl)acetamide, N-Acetyl-p-aminophenol. The chemical name for ibuprofen is (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Both active substances comply with the Ph.Eur. requirements, i.e. with the Ph.Eur. monograph 0049 for paracetamol and Ph.Eur. monograph 0721 for ibuprofen. CEP certificates were submitted for all active substance sources.

II.3 Medicinal Product

The aim of the development of Paracetamol 25 mg/ml + Ibuprofen 20 mg/ml oral suspension was to obtain a combination drug product containing paracetamol and ibuprofen with a suitable dosage form and dosage strength for the oral administration to the paediatric population and, simultaneously, having an immediate release of active substances in order to produce a faster therapeutic effect.

Excipients used in the formulation are glycerol, sodium benzoate, sodium citrate, anhydrous citric acid, sodium chloride, polysorbate 80, xanthan gum, aluminium magnesium silicate, sucralose, isomalt, orange flavour, ethanol and purified water. The quality of each excipient was demonstrated. The quantities of excipients with known effect follow the applicable requirements and, as required, they are included in the approved SmPC.

The manufacturing process was divided in several steps which ensure the homogeneity, stability and quality of the final product. The finished product is manufactured by sequential suspending of active substances and excipients in purified water, bulk filtration and filling in the primary container. Manufacturing process was satisfactorily validated.

The finished product is controlled against a finished product specification consisting of standard parameters for this type of dosage form.

The relevant stability data were provided. The approved shelf-life of the medicinal product is 24 months. Storage conditions: This medicinal product does not require any special storage conditions. The shelf-life after the first opening is 6 months.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product was presented in a suitable manner. The results of tests carried out indicate 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 clinical use.

The quality of the product is considered acceptable when used in accordance with the conditions defined in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Marketing Authorisation Holder declares that active substances, paracetamol and ibuprofen, are available on the market for more than 45 years and acquired data of its biochemistry, pharmacology and toxicology are comprehensive. As ibuprofen and paracetamol are widely used, well-known active substances, the applicant has not provided additional studies. The Non-clinical overview based on literature review is adequate. The proper justification of Non-clinical summary necessity was made and is considered appropriate. The expert is considered qualified. Ibuprofen and paracetamol are well-known active substances. This marketing authorization application meets all criteria for well-established use application according to the Article 10a of Directive 2001/83/EC. Due to the character of well-established use application, submission of no new studies by the applicant is acceptable. This marketing authorization application is based on literature references only. Pharmacokinetic, pharmacodynamic and toxicology data are sufficient.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Applicant submitted Phase I and Phase II of ERA. Considering the submitted data, ibuprofen should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

III.3 Discussion on the non-clinical aspects

Submitted non-clinical data are adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a well-established use national application according to Article 10a of Directive 2001/83/EC, so called bibliographical application. Applicant confirmed that the combination of paracetamol and ibuprofen is a thoroughly investigated substance that has been in well-established medicinal use within the Community for at least ten years which is true as both active substances have been in use for tens of years, alone as well as in combination.

IV.2 Pharmacokinetics

Both paracetamol and ibuprofen are rapidly absorbed from the gastrointestinal tract, with the maximum plasma concentration occurring about 10 to 60 minutes after oral administration.
The rate and absorption of both paracetamol and ibuprofen from the combined drug are slightly delayed when administration occurs after eating food. Food reduces the peak plasma concentration and delays the time to reach peak plasma concentration.
As with any medicine that contains paracetamol, it is distributed to most body tissues. Plasma protein binding of paracetamol is negligible at usual therapeutic concentrations, however, this binding increases with increasing concentration. Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.
Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly in the form of inactive glucuronide and sulfated conjugates. Less than 5% is excreted in the unchanged form. The metabolites of paracetamol include a minor hydroxylated intermediate that has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione; however, it can accumulate after paracetamol overdose and, if left untreated, has the potential to cause severe and even irreversible liver damage.
Paracetamol is metabolised differently by premature children, new-borns and young children compared to adults, with the sulfated conjugate being the predominant form.
Ibuprofen is metabolised in the liver into two major metabolites which, together with a negligible amount of unchanged ibuprofen, are primarily excreted by the kidney alone or as conjugates.
The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions in which the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate this possibility found no potential drug interactions at the level of metabolic pathways.
The elimination half-life of paracetamol varies between 1 and 3 hours. Paracetamol crosses the placenta and is distributed into human milk in small quantities following oral administration. Data from more than 15 nursing women suggest that approximately 1–2% of the maternal daily dosage would be ingested by a nursing infant.
There appears to be little, if any, distribution of ibuprofen into breast milk. Limited data indicate that ibuprofen is distributed into milk, resulting in infant exposures of 0.06–0.6% of the maternal weight-adjusted daily dosage.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: 2.10 Central Nervous System. Analgesics and antipyretics; ATC code: N02BE51 - Nervous system. Analgesics. Other analgesics and antipyretics. Anilides. Paracetamol, combinations excluding psycholeptics.

The pharmacological actions of ibuprofen and paracetamol differ in place and mode of action. These complementary modes of action are synergistic, resulting in a greater analgesic and antipyretic effect compared to ibuprofen or paracetamol in monotherapy.

The exact location and mechanism of paracetamol's analgesic action are not clearly defined. Paracetamol's exact mechanism of action is still not completely defined. Paracetamol has central and also peripheral mode of action.
Ibuprofen is a derivative of propionic acid with analgesic, anti-inflammatory and antipyretic activity. As an NSAID, the drug's therapeutic effects result from its inhibitory effect on the enzyme cyclooxygenase, leading to a reduction in prostaglandin synthesis.

IV.1 Clinical efficacy

The applicant did not present own clinical studies to determine efficacy and safety of combination of paracetamol and ibuprofen. To prove the efficacy and safety of the combination, the scientific literature was screened to identify published controlled clinical studies and reviews.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore, efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache. Based on the submitted data, the indication "the short-term symptomatic treatment of acute moderate pain in adults and adolescents over 12 years of age" is supported.

IV.2 Clinical safety

Applicant submitted sufficient amount of data from the referenced studies and other products available on the market to support the claim that the safety of the proposed product is acceptable to grant the marketing authorisation. All relevant safety issues and adverse events has been listed in the proposed SmPC and PIL.

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 Paracetamol/Ibuprofen Reclinmed.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

Submitted clinical data are adequate to support the indication "the short-term symptomatic treatment of acute moderate pain in adults and adolescents over 12 years of age".

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 PIL was English.
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

The benefit/risk assessment is considered positive.
The dossier is generally well presented and all processes appear to be well controlled. The application is acceptable from the quality perspective.
There are no objections to the dossier of Paracetamol/Ibuprofen Reclinmed from a non-clinical point of view.
From the clinical perspective, submitted clinical data are adequate to support the indication.