LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ibuprofen Mylan
(ibuprofen)

SE/H/1890/01-02/DC

This module reflects the scientific discussion for the approval of Ibuprofen Mylan. The procedure was finalised on 2020-01-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Mylan AB has applied for a marketing authorisation for Ibuprofen Mylan, 200 mg/10 ml and 400 mg/10 ml, oral suspension in sachet. The active substance is ibuprofen belongs to the group of non-steroidal anti-inflammatory and analgesic drug (NSAIDs) and has a well characterised analgesic, anti-inflammatory and anti-pyretic effects.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well known. As ibuprofen is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment

Ibuprofen Mylan 200 mg and 400 mg oral suspension is not considered to increase the risk to the environment beyond or above that which may be caused by other ibuprofen-containing products.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen has been studied extensively in adults and children in a variety of painful and inflammatory conditions where its therapeutic effects are comparable to other NSAIDs and paracetamol. A number of large clinical trials have focused on the clinical uses, safety and pharmacological properties of ibuprofen given at prescription level doses (<2,400 mg/day) compared with newer NSAIDs (including coxibs). In many of these studies, ibuprofen was used as a reference drug.

IV.2 Pharmacokinetics

The pharmacokinetic properties of ibuprofen are well known. The Applicant has shown that Ibuprofen Mylan has similar composition and similar *in vitro* dissolution as two other oral ibuprofen suspensions on the market for which there are clinical pharmacokinetics data available. These formulations are shown to have similar drug exposure as other established oral ibuprofen formulations (e.g., tablets and suspensions). Literature data on efficacy and safety come from different ibuprofen formulations (mainly oral tablets). The Applicant has provided acceptable evidence and discussions how the expected exposure from the applied product is bridged to the exposure / efficacy / safety presented in the literature.

IV.3 Pharmacodynamics

Ibuprofen Mylan is a non-steroidal anti-inflammatory and analgesic drug (NSAID) with well-characterised analgesic, anti-inflammatory and anti-pyretic effects. The inhibitory effect on the enzyme cyclooxygenase results in reduced prostaglandin synthesis. The literature summary on pharmacodynamics was mainly based on narrative reviews and some experimental studies. The primary and secondary pharmacology of ibuprofen is considered well-known and adequately summarised in the application.

IV.4 Clinical efficacy

The indication is for short term symptomatic relief of mild to moderate pain and/or fever in adult and children above 6 years old (>20 kg). To support this, the clinical efficacy was determined based on published clinical trials, epidemiological studies and meta-analyses evaluating the effects of ibuprofen in the relief of all grades of pain, inflammation and/or fever in a wild range of conditions, including rheumatic and other musculoskeletal conditions, upper respiratory tract conditions (colds, influenza), dental pain, surgery, dysmenorrhea and general headaches. Efficacy data for the treatment of pain and fever in children 2-18 years old has also been reviewed.

The recommended dose range in adults and adolescents older than 12 years is 200-400 mg with maximum daily dose of 1200 mg. The proposed dose range in children 6-12 years old is a daily dose of 20-30mg/kg of body weight with a maximum daily dose of 600-800mg. The volume in the sachet cannot be divided which makes the product unsuitable for treatment of children under 6 years of age (<20kg).

IV.5 Clinical safety

The safety profile has been adequately characterized based on published clinical and epidemiological studies. The known adverse effects on cardiovascular, gastro-intestinal, kidney, liver and coagulation systems have been discussed. The product information reflects the known level of cardiovascular and other risks for NSAIDs as a class. No new safety concerns have been identified based on the reviewed data.

IV.6 Risk Management Plans

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 Ibuprofen Mylan.

Safety specification

The Risk management Plan has been updated in line with the safety concerns available in the Mylan RMP version 2.1 approved via work-sharing procedure on 30-Nov-2018 for ibuprofen Decentralised, Mutual Recognition and National procedures (DE/H/2597, SE/H/0912/R/001 and 13/H/0024/001-002). The safety specification is acceptable.

Summary of safety concerns	
Important identified risks	• Gastrointestinal bleeding, ulceration or perforation • Cardiovascular risk • Severe skin reactions • Renal disorders
Important potential risks	• Interaction with low-dose aspirin (Reduction of cardioprotective effect of low-dose aspirin)
Missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.1 signed 01-May 2019 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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

Ibuprofen is a non-selective inhibitor of cyclo-oxygenase, leading to reduce synthesis of prostaglandins. Ibuprofen has been marketed as an analgesic and anti-inflammatory drug since the 1960's.

The submitted literature data gives an overview of the current knowledge of the beneficial effects of ibuprofen. The available data also supports the recommended posology. The Applicant has sufficiently shown that the use of ibuprofen in the applied indications is well established. The use of this pharmaceutical presentation of ibuprofen is considered appropriate from 6 years of age. The Applicant´s overview of clinical safety provides sufficient support for the information in the SmPC. No new safety concern has been identified.

The benefit-risk balance is considered positive and Ibuprofen Mylan, 200 mg/10 ml and 400 mg/10 ml, oral suspension in sachet, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Ibuprofen Mylan, 200 mg/10 ml and 400 mg/10 ml, oral suspension in sachet, was positively finalised on 2020-01-29.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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