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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Remedica (UK) Limited Marketing Authorisations (licences) for the medicinal product Ibuprofen 400mg Coated Tablets (PL 11125/0018 and PL 11125/0019) on 9th June 2010. This is a prescription-only medicine (POM) for the treatment of headache, migraine, dental pain, backache, rheumatic and muscular pain, neuralgia, ankylosing spondylitis, soft tissue injuries, rheumatoid arthritis and osteoarthritis.

Ibuprofen 400mg Coated Tablets contain the active ingredient ibuprofen, which belongs to a class of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It relieves pain, lowers temperature and reduces inflammation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ibuprofen 400mg Coated Tablets outweigh the risks; hence, Marketing Authorisations have been granted.
IBUPROFEN 400MG COATED TABLETS
PL 11125/0018-19

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Remedica (UK) Limited Marketing Authorisations (licences) for the medicinal product Ibuprofen 400mg Coated Tablets (PL 11125/0018 and PL 11125/0019) on 9th June 2010. The product is a prescription-only medicine (POM), indicated for rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of cold and influenza.

These are applications for Ibuprofen 400mg Coated Tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The UK reference product is Brufen 400mg Tablets (PL 00037/0334), originally granted to Knoll Pharma Limited on 16th December 1992; but currently authorised to Abbott Laboratories Ltd after a change of authorisation holder on 15th February 2002. Ibuprofen has a well-established use in the management of pain relief and reducing inflammation. The current applicant already hold a marketing authorisation for Ibuprofen 200mg Coated Tablets (PL 11125/0001), approved 12 June 1992.

The active ingredient ibuprofen is a member of a class of medicines called, non-steroidal anti-inflammatory (NSAIDs). Ibuprofen relieves pain, lowers temperature and reduces inflammation. It is effective in the relief of headaches, rheumatic pain, muscular pain, backache, cold, flu symptoms, migraine, period, pain, dental pain and neuralgia.

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys. No new pre-clinical or clinical efficacy studies were conducted for these applications.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements, and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder (MAH) has provided adequate justification for not submitting a detailed Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a new strength of an approved product and it is not likely to change the total market of ibuprofen. As the application is for a product with the same clinical indications as an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Ibuprofen
INN/ BAN: Ibuprofen
Chemical name: 2-(4-isobutylphenyl) propionic acid.
Structure:

Molecular formula: C_{13}H_{18}O_{2}
Molecular weight: 206.28

General Properties
Appearance: White crystalline powder or colourless crystals.
Chirality: Racemic

The active substance, ibuprofen, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of the active substance ibuprofen are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

A suitable retest period has been stated, based on stability data from batches of the active substance stored in-line with current requirements and in the proposed packaging.

DRUG PRODUCT
Other ingredients
The drug product is a coated tablet, containing 400mg ibuprofen. The tablets are pink and biconvex in appearance.

Other ingredients in the tablet core consist of pharmaceutical excipients, namely microcrystalline cellulose, sodium starch glycolate (type A), pre-gelatinised starch, colloidal anhydrous silica and purified talc.

Ingredients in the tablet coating consist of the pharmaceutical excipients, namely gelatin, macrogol 6000, povidone (PVP), sucrose, calcium carbonate, purified talc, erythrosine (E127), carnauba wax, beeswax, spermaceri wax and trichloroethylene.
All the ingredients used in the coating comply with their respective European pharmacopoeia monographs, with the exception of erythrosine E127, spermaceti wax and trichloroethylene, which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all the excipients.

None of the excipients used in the tablet core or tablet coating contain material of animal or human origin, with the exception of gelatin. A satisfactory EDQM certificate of suitability has been provided for the supplier of gelatin, showing that they comply with current regulations concerning the minimisation of transmission of TSE/BSE.

**Pharmaceutical Development**

Suitable pharmaceutical development data have been provided for these applications. The physico-chemical properties of the drug product have been compared with the reference product. These data demonstrate that the proposed product can be considered a generic medicinal product to Brufen 400mg Tablets (Abbott Laboratories Ltd).

**Bioequivalence**

The applicant has submitted satisfactory dissolution data for the current formulation versus the reference product Brufen 400mg Tablets (Abbott Laboratories Limited). The drug product is a direct scale-up version of the applicant’s already licensed product Ibuprofen 200mg Tablets (PL 11125/0001), which was originally granted a licence in 1992. In-line with the “Guideline on the Investigation of Bioequivalence” CHMP/EWPQWP/1401/98, and the data submitted in support of the application, it is considered that a bioequivalence study is not required for this current application.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data for three consecutive commercial-scale batches have been provided and are satisfactory.

**Finished product specification**

The finished product specification is satisfactory and provides assurance of the quality of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for three production-scale batches of the product and demonstrate compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The finished product is licensed for marketing in aluminium/polyvinylchloride (PVC) blister strips, each holding 10 or 12 sugar-coated tablets. These blister strips are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 36, 48, 60, 72, 84 and 100 tablets. Specifications and Certificates of Analysis for all packaging
types used have been provided and are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 5 years has been set, which is satisfactory. Storage instructions are “Store below 25°C”, “Store in the original container”, and “Keep the container in the outer carton”.

**Quality Overall Summary**
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified person.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL, and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille.

**MAA form**
The MAA forms are pharmaceutically satisfactory.

**Conclusion**
The grant of marketing authorisations for these applications is recommended.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory.

The grant of marketing authorisations for these applications is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of ibuprofen is well-known. No new pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

The applicant has submitted satisfactory dissolution data for the current formulation versus the reference product Brufen 400mg Tablets (Abbott Laboratories Limited). The drug product is a direct scale-up version of the applicant’s already licensed product Ibuprofen 200mg Tablets (PL 11125/0001), which was originally granted a licence in 1992. The data submitted in support of the application is considered to be satisfactory and no bioequivalence study is required for this current application.

EFFICACY
No new data are submitted and none are required for these applications. Efficacy is reviewed in the clinical overview. Ibuprofen is considered to have a particularly wide therapeutic index and its efficacy is well-established from its extensive use in clinical practice.

SAFETY
No new safety data have been submitted and none are required for these applications. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of ibuprofen is well-known and ibuprofen is widely considered to be one of the best tolerated NSAIDs.

EXPERT REPORT
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified person. The Clinical Expert report states that ibuprofen has a wide therapeutic range and a low margin of toxicity. A literature search has revealed no evidence of differences in bioavailability or presents a clinical hazard.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product, and is acceptable.

Patient Information Leaflet (PIL)
The final PIL is consistent with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

CONCLUSION
The grant of marketing authorisations for these applications is recommended.
OVERALL CONCLUSION AND BENEFIT:RISK ASSESSMENT

QUALITY
The important quality characteristics of Ibuprofen 400mg Coated Tablets are well-defined and controlled. The specification and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit:risk ratio.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of ibuprofen is well-established from its extensive use in clinical practice. Ibuprofen has been used as a treatment for pain relief, reducing inflammation and lowering temperature for over 50 years.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory.

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 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT:RISK ASSESSMENT
The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk ratio is considered to be positive.
**IBUPROFEN 400MG COATED TABLETS**  
**PL 11125/0018-19**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 27(^{th}) June 2003.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 7(^{th}) December 2005.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 7(^{th}) December 2005, 20(^{th}) September 2006 and 20(^{th}) August 2008.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 22(^{nd}) May 2006, 24(^{th}) October 2006 and 17(^{th}) May 2010.</td>
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<td>5</td>
<td>The application was determined on 8(^{th}) June 2010.</td>
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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

The following table lists non-safety updates to the Marketing Authorisation for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tr>
<td>04/04/2011</td>
<td>IB</td>
<td>To update section 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9 and 5.1 of the SmPC, to include additional safety information, as requested by the MHRA on the 31-01-2007 with regards to cardiovascular safety warnings for NSAIDs, also following a request by the MHRA on the 30-01-2008 to update minimum particulars for NSAIDS and on the 30-10-2008 to implement SmPC changes following discussions at the Pharmacovigilance Working Party. Consequentially, the PIL has been updated.</td>
<td>Granted 06/07/2012</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
IBUPROFEN 400MG COATED TABLETS
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CARTON
Below is a colour-mock-up of the outer packaging and is representative of the other pack sizes in the range.

Blister Foil