IPAR

IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Nuasa 75mg Gastro-resistant Tablets

Acetylsalicylic Acid (Aspirin)

PA1455/3/1

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Nuasa 75 mg Gastro-resistant tablets, from Uniphar plc. on 14th October 2011 for decreasing the risk of myocardial infarction in patients with angina pectoris, relapse prophylaxis after myocardial infarction, prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery and for the secondary prevention of transient ischaemic attacks (TIA) and stroke.

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC and is referred to as a 'well-established use' application. This means that the product contains a drug substance (aspirin) which has such a well-established use and an acceptable level of safety that the marketing authorisation holder (MAH) are permitted to submit published data to support the safety and efficacy aspects of their application.

Nuasa 75mg is subject to medical prescription, supply through pharmacies only.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/.

Name of the product	Nuasa 75mg Gastro-resistant Tablets
Name(s) of the active substance(s) (INN)	Acetylsalicylic acid (Aspirin)
Pharmacotherapeutic classification (ATC code)	B01AC06
Pharmaceutical form and strength(s)	75mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1455/3/1
Marketing Authorisation Holder	Uniphar plc

II QUALITY ASPECTS

II.1. Introduction

This application is for Nuasa 75 mg Gastro-resistant Tablets.

II.2 Drug substance

The active substance is Acetylsalicylic acid which is more commonly known as aspirin and is an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Nuasa are white, round and biconvex gastro-resistant tablets. Gastro-resistant tablets are delayed-release tablets that are intended to resist the gastric fluid and to release the active substance (aspirin) in the intestinal fluid. This is ensured by the gastro-resistant coating which covers the tablet.

Each gastro-resistant tablet contains 75 mg aspirin (acetylsalicylic acid). The other ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica and potato starch. The gastro-resistant coating contains talc, glycerol triacetate and methacrylic acid-ethylacrylate copolymer (1:1) dispersion 30%.

The tablets are packaged in PVC/ aluminium blisters with 30, 90 and 500 tablets per package. Not all pack sizes may be marketed.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. and are therefore adequately controlled by the agreed specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for gastro-resistant tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in PVC/ aluminium blisters containing 30, 90 or 500 tablets per package.

Evidence has been provided that the blisters comply with the relevant Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

product for 2 years when stored at below 30°C and kept in the outer carton in order to protect the tablets from light and moisture.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Nuasa 75 mg Gastro-resistant tablets. Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the

III NON-CLINICAL ASPECTS

III.1 Introduction

The application was submitted as a bibliographic application, for an active of well established use, according to Article 10(a) of Directive 2001/83/EC (as amended).
No new preclinical data have been supplied with this application and none are required for an application of this type.

IV CLINICAL ASPECTS

The application was submitted as a bibliographic application, for an active of well established use, according to Article 10(a) of Directive 2001/83/EC (as amended).
No new clinical data have been supplied with this application and none are
required for an application of this type.

Nuasa 75mg Gastro-resistant Tablets indicated for:

- Decreasing the risk of myocardial infarction in patients with stable and unstable angina pectoris.
- Secondary prophylaxis after myocardial infarction.
- Prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery.
- The secondary prevention of transient ischaemic attacks (TIA) and stroke provided that intracerebral haemorrhages have been ruled out.

IV.2 Pharmacokinetics

After the application as gastro-resistant formulation, ASA is absorbed in the duodenum. Maximum plasma levels are achieved 3 hours after administration. ASA is hydrolised enzymatically to salicylic acid in the intestinal mucosa, but predominantly in the liver. Furthermore, salicylic acid is glucuronised in the liver.

ASA gastro-resistant tablets are bioequivalent with a hydrous solution of ASA; due to the particular pharmaceutical form, the half-life is prolonged from 2 to 4 hours.
Excretion of salicylic acid (85 % in alkaline and 10 % in acid urine) as well as its conjugates and derivates happens mainly renal.

IV.3 Pharmacodynamics

No new data has been submitted, however, an overview on published data on the pharmacodynamics of acetylsalicylic acid has been provided.

The mechanism of action of ASA is well known and has been satisfactorily summarised by the applicant. The antithrombotic effect of ASA is based on the inhibition of thromboxane A2-synthesis in thrombocytes. The action of ASA on platelet is permanent, lasting for the life of the platelet (7 to 10 days). Repeated, low, doses of ASA therefore produce a cumulative inhibitory effect on platelet function.

IV.4 Clinical Efficacy

The applicant has provided an overview on the efficacy of ASA in the sought indications, based on published literature. The most important publication is the large meta-analysis and the current European guidelines for the prevention of cardiovascular diseases.

The data provided supports the well-established efficacy and use of ASA in the indications:
- Decreasing the risk of myocardial infarction in patients with stable and unstable angina pectoris.
- Secondary prophylaxis after myocardial infarction.

- Prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery.
- The secondary prevention of transient ischaemic attacks (TIA) and stroke provided that intracerebral haemorrhages have been ruled out. There are no regular dose-finding studies for ASA available in these indications. The recommended dose for the prevention of cardiovascular events has been adjusted towards lower levels (75-150 mg daily) for all indications except after coronary bypass, where the lowest recommended dose is 100 mg daily.

The dosing recommendation in the treatment and prevention of cerebrovascular events is still a matter of debate; however, a recommendation of a daily dose between 75 and 150 mg (and upto 300mg for *Prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery*) is supported by both clinical and pharmacodynamic data as well as current guidelines.

The SPC has been updated to reflect the posology as recommended in the submitted publications and current European guidelines.

IV.5 Clinical Safety

The safety profile for ASA is well known and has been comprehensively described in the literature. The applicant has provided a broad summary of the data.

The safety aspects are adequately reflected in the SPC.

The MAH has provided adequate justification for not submitting a Risk Management Plan. There are no ongoing safety concerns with this well established active that require additional risk - management activates.

The PSUR submission scheme should follow Volume 9A of The Rules Governing Medicinal Products in the European Union.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

The application was submitted as a bibliographic application, for an active of well established use, according to Article 10(a) of Directive 2001/83/EC (as amended).
No new clinical data have been supplied with this application and none are
required for an application of this type.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
Acetylsalicyclic acid (Aspirin) is an active substance of well known safety and efficacy. It is used for a number of decades in the EU.

From a quality and clinical perspective the overall assessment outcome for Nuasa 75 mg Gastro-resistant tablets is positive.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted, considered that Nuasa 75 mg Gastro-resistant tablets demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI REVISION DATE

October 2011