IPAR

IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Minodene 50mg Film-coated Tablets

MINOCYCLINE HYDROCHLORIDE DIHYDRATE

PA 0126/177/001

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 Minodene 50mg Film-coated Tablets (MINOCYCLINE HYDROCHLORIDE DIHYDRATE) from 25th June 2010 to Clonmel Healthcare Limited for indications as per section 4.1 of the SPC as follows:

Minocycline is a broad spectrum antibiotic used for the treatment of infections caused by tetracycline-sensitive organisms. Some tetracycline resistant strains of Staphylococci are also sensitive.

Minodene tablets are indicated for the treatment of ear, nose and throat infections, acute and chronic bronchitis, bronchiectasis, lung abscess, pneumonia, prostatitis, venereal diseases, urinary tract infections, salpingitis, skin and soft tissue infections, acne, ophthalmological infections, nocardiosis, and for the prophylactic treatment of asymptomatic meningococcal carriers.

This application for Minodene 50mg Film-coated tablets was submitted as a New National generic application in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at file://imbsrv-dmsprod/imbdocs3/001/002/063/www.imb.ie

Name of the product	Minodene 50mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	MINOCYCLINE HYDROCHLORIDE DIHYDRATE
Pharmacotherapeutic classification (ATC code)	J01AA08
Pharmaceutical form and strength(s)	50mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA126/177/1
Marketing Authorisation Holder	Clonmel Healthcare Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Minodene 50mg Film-coated Tablets.

II.2 Drug substance

The active substance is minocycline hydrochloride dihydrate, 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

The product is formulated as a film-coated tablet containing 50mg of minocycline hydrochloride dehydrate.

The product also contains the following excipients:
Tablet core
Povidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate.
Coating
Hypromellose, Macrogol, Iron Oxide Yellow (E172), Titanium Dioxide (E171).

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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with a Ph. Eur. monograph where one exists or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the BP monograph for Minocycline 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 as PVC/PVDC-Aluminium blisters.

Evidence has been provided that the components of the blister comply with Ph. Eur. requirements/EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years when stored at a temperatire not exceeding 25°C.

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 Minodene 50mg Film-coated Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for several years. No new preclinical data have been submitted as preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

III.2 Pharmacokinetics

Minocycline hydrochloride is readily absorbed from the gastrointestinal tract and is not significantly affected by the presence of food or moderate amounts of milk, although absorption is impaired by the concomitant administration of iron salts or antacids containing calcium, magnesium or aluminium salts. As minocycline hydrochloride is more lipid-soluble than doxycycline and other tetracyclines it is widely distributed in body tissues and fluids, including the cerebrospinal fluid.

About 75% of minocycline hydrochloride in the circulation is bound to plasma proteins; its half life ranges from 11 to 23 hours. The plasma half life tends to be prolonged in patients with severe renal impairment.

III.3 Discussion on the non-clinical aspects

As this is a generic medicine and Minocycline is a well known active substance with established efficacy and tolerability it is acknowledged that an abridged application in this respect thus avoids the need for repetitive tests on animals and humans.

IV CLINICAL ASPECTS

IV.1 Introduction

Minocycline is a well known active substance with established efficacy and tolerability.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

Based on the pharmacokinetic parameters of the active substance, the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Guidance.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption: Minocycline hydrochloride is readily absorbed from the gastrointestinal tract and is not significantly affected by the presence of food or moderate amounts of milk, although absorption is impaired by the concomitant administration of iron salts or antacids containing calcium, magnesium or aluminium salts.

Distribution: As minocycline hydrochloride is more lipid-soluble than doxycycline and other tetracyclines it is widely distributed in body tissues and fluids, including the cerebrospinal fluid.

Excretion: About 75% of minocycline hydrochloride in the circulation is bound to plasma proteins; its half life ranges from 11 to 23 hours. The plasma half life tends to be prolonged in patients with severe renal impairment.

IV.3 Pharmacodynamics

Minocycline hydrochloride, a semi-synthetic derivative of tetracycline, is a broad spectrum antibiotic used for the treatment of infections caused by tetracycline-sensitive organisms. Some tetracycline resistant strains of staphylococci are also sensitive.

Minocycline has a long serum half-life and can be administered at 12 hour intervals.

Minocycline interferes with the third stage of bacterial protein synthesis. After amino acids are activated and attached to t-RNA (transfer RNA), the resulting amino acyl-t-RNA migrates to the bacterial ribosome for synthesis of proteins. Minocycline binds to the 30s subunit on the ribosome and inhibits binding of the aminoacyl-t-RNA molecules.

IV.4 Clinical Efficacy

The clinical efficacy of minocycline is well established.

IV.5 Clinical Safety

A Risk Management Plan is not proposed at this time in line with the known safety profile of the active substance.

The schedule for Periodic Safety Update Reports (PSUR) submission has been addressed in line with this being a generic product. As minocycline is a well-established product with a known safety-profile, a 3-year-cycle for PSUR submission has been agreed.

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.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Minodene 50mg Film-coated tablets are a generic medicinal product. Minocycline is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

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 Minodene 50mg Film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.