Public Assessment Report

Scientific discussion

Mirtazapin "Merck NM"
Mirtazapine

DK/H/0986/001-003/DC

This module reflects the scientific discussion for the approval of Mirtazapin "Merck NM". The procedure was finalised at 19 April 2007. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This assessment report concerns Mirtazapin “Merck NM”, Generics UK Ltd., orodispersible tablets 15 mg, 30 mg and 45 mg, approved in a Decentralised Procedure on 19th April 2007.
The Reference Number for the Decentralised Procedure is DK/H/0986/001-003/DC.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mirtazapin “Merck NM” orodispersible tablets, in the treatment of depression, could be approved.

The application for Mirtazapin ”Merck NM” 15 mg, 30 mg and 45 mg orodispersible tablets is an abridged generic application made according to Article 10(1) of Directive 2001/83/EC submitted within the decentralised procedure with Denmark acting as reference member state (RMS) and BE, CZ, DE, ES, FI, FR, IE, IT, NL, NO, PL, PT, SE, UK as the concerned member states (CMS).

Essential similarity to the nationally authorised reference innovator product Remeron Smelt 15 mg, 30 mg and 45 mg tablets, marketed by N.V. Organon is claimed. The medicinal product used for the bioequivalence study is Zispin SolTab 45 mg orodispersible tablets marketed by Organon Laboratories Ltd. and purchased from the UK market.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all of the sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form: Orodispersible tablets.
Active substance: Mirtazapine.
Strength: 15mg, 30 mg and 45 mg mirtazapine.
Excipients: Crospovidone; Mannitol; Cellulose, microcrystalline; Aspartame; Silica, colloidal anhydrous; Magnesium Sterate; Strawberry Guarana Flavour; Peppermint Flavour.
Shelf life: 24 months.
Special precautions for storage: This medicinal product does not require any special storage conditions.
Nature and content of container: PVC/Polyamide/Aluminium/Polyester blister packs. Pack sizes: 6, 12, 16, 30, 48, 60, 90, 96 orodispersible tablets.

II.2 Drug Substance

Active Substance: Mirtazapine.
The active substance is not described in the European Pharmacopoeia. It is a white to creamy white crystalline powder. The melting point is between 114 - 117°C. It is freely soluble in methanol and dichloromethane. Specific rotation -0.5° to +0.5°.

The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed re-test period of 36 months is justified.

II.3 Medicinal Product

Mirtazapine "Merck NM" orodispersible tablets is formulated using excipients described in the current Ph. Eur, except for Strawberry guarana Flavour and Peppermint Flavour which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

The finished product is presented in 3 strengths of white round orodispersible tablets, to be marketed in Alu/Alu-blister packaging. 15mg tablets are embossed with "36" on one side and 'A' on the other side, 30mg tablets are embossed "37" on one side and 'A' on the other side and 30mg tablets are embossed with "38" on one side and 'A' on the other side. Each tablet contains 15 % of the active substance. The 3 strengths are formulation proportionals.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

It is acceptable to the RMS that studies have not been performed, as the application is submitted in accordance with Article 10 of Directive 2001/83/EC.

IV.2 Pharmacokinetics

Absorption

After oral administration of mirtazapine orodispersible tablets, the active substance mirtazapine is rapidly and well absorbed (bioavailability about 50%), reaching peak plasma levels after 1 - 2 hours. Food intake has no influence on the pharmacokinetics of mirtazapine.

Metabolism/elimination

The mean half-life of elimination is 20 - 40 hours; longer half-lives, up to 65 hours, have occasionally been recorded but in young men the half-lives have been shorter. The elimination half life is sufficient to justify administration once daily. Mirtazapine is almost completely metabolized and eliminated within a few days with urine and faeces. Biotransformation mainly occurs through demethylation and oxidation and subsequent conjugation. In vitro

Studies of human liver microsomes show that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the mirtazapine 8-hydroxy metabolite, whereas the CYP3A4 enzyme is assumed to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active, and its pharmacokinetic profile is similar to that of non-metabolized drug.

IV.3 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further data have been submitted or are considered necessary.

The application concerns three dosage strengths, i.e. 15 mg 30 mg and 45 mg, to support the application, the applicant has submitted a single bioequivalence study performed using the 45 mg strength tablet. The applicant justifies the biowaver request by demonstrating compliance with section 5.4 of the Bioequivalence guideline. The RMS concurs that a biowaiver is justifiable.

The three strengths are manufactured by the same manufacturer, the qualitative composition is the same with the exception of the ratio of amount of active substance and excipients are the same.

The study was an open label, two-treatment, two periods, two sequence, single dose, crossover study conducted under fasting conditions with a wash out period of 12 days between administrations. 45 mg was administered in each period with 240ml water. Subjects were confined to the clinical research centre from at least 10 hours prior to drug administration until 36 hour post-dose blood draw in each period. Water was permitted ad lib until 1 hour before dosing and again 1 hour after dosing.

Mirtazapine orodispersible tablets 45 mg manufactured by Aurobindo Pharma Ltd, India has been tested against Zispin SolTab 45 mg tablets, Organon Laboratories Ltd., UK, from the UK market.

24+4 healthy volunteers were randomised into the study and 24 completed (all male, 20-41 years, 50-70kg). There were 4 dropouts, subjects 8, 10 and 14 due to positive testing for benzodiazepines in period II and subject 21 who vomited after dosing in period II.

Based on the submitted bioequivalence study Mirtazapine Merck NM Orodispersible tablets 15mg, 30mg and 45mg are considered bioequivalent with Remeron tablets with respect to rate and extent of absorption of mirtazapine. Tolerability of the test product is acceptable and not significantly different from reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Mirtazapine “Merck NM”, 15 mg, 30 mg and 45 mg, orodispersible tablets was successfully finalised on19 April 2007.