Public Assessment Report

Scientific discussion

Paroxetin "HEXAL"
Paroxetine hydrochloride anhydrate

DK/H/0233/003-004/MR

Applicant: HEXAL

This module reflects the scientific discussion for the approval of Paroxetin "Hexal". The procedure was finalised at 20 June 2006. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This assessment report concerns Paroxetin "Hexal", film-coated tablets 10 mg and 30 mg, which are line extensions to the generic product Paroxetin "Hexal", film-coated tablets 20 mg and 40 mg, approved in MRP 28 May 2001 (DK/H/0233/001-002).

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Paroxetin "Hexal", in the treatment of Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with or without agoraphobia, Social Anxiety Disorder/Social phobia, Generalised Anxiety Disorder and Post-traumatic Stress Disorder, could be approved.

A national Danish licence for Paroxetin "Hexal", film-coated tablets 10 mg and 30 mg was granted 27th June 2005, together with licences for the products Paroc, Optipar and Paroneurin, film-coated tablets, 10 mg and 30 mg, which are all based on identical dossiers.

The legal base for the Marketing Authorisations in Denmark is Directive 2001/83/EC as amended; Article 10.3 (previously Article 10.1(a)(iii), last paragraph) for 10 mg – so called "Hybrid application" and Article 10.1 (previously Article 10.1(a)(iii), first paragraph) for 30 mg – so called "generic application".

Paroxetin "Hexal", film-coated tablets 20 mg and 40 mg has been judged to be equivalent and thus essential similar to the Brand leader Seroxat from GlaxoSmithKline Pharma A/S.

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

Paroxetin "Hexal":
Pharmaceutical form: Tablets, film coated.
Active substance: Paroxetine hydrochloride anhydrate.
Strength: 10 mg and 30 mg paroxetine
Excipients: Mannitol, Cellulose, microcrystalline, Copovidone
Sodium starch glycollate (Type A), Silica, colloidal anhydrous,
Magnesium stearate, Hypromellose 5 cps, Talc (micronised),
Titanium dioxide (E171),
30 mg tablets: Ferric oxide (E172), Indigotine (E132)
Shelf life: 18 months for the 10 mg strength and 36 months for the 30 mg strength.
Special precautions for storage: Do not store above 30°C.
Nature and content of container: PVC-aluminium blister and Polyethylene (PE/HD) container and closure.

II.2 2.2 Drug Substance

General information
Active Substance: Paroxetine hydrochloride, anhydrate.
The active substance is not described in the European Pharmacopoeia, but a draft monograph was published in Pharmeuropa vol. 16.2, April 2004. A Ph. Eur. monograph for paroxetine HCl hemihydrate exists. Paroxetine HCl anhydrate is official in the USP.

It is acceptable that the specification of paroxetine hydrochloride, anhydrous complies with the draft monograph until an official monograph is published in the Ph. Eur. Afterwards, the applicant is asked to submit a variation application in order to comply with the monograph described in the European Pharmacopoeia.

The active substance is a white to off-white powder. It is hygroscopic and shows polymorphism. It is soluble in methanol, slightly soluble in water, sparingly soluble in dichloromethane and ethanol. The substance contains two chiral centres and 4 isomers are possible. Paroxetine is the trans (-) configuration.

Manufacture and characterisation
The documentation on the active substance is presented as an EDMF/ASMF (in CTD-format). The Applicant's Part of the EDMF/ASMF has been forwarded by the Applicant. The Applicant's and Restricted Part plus a LoA have been forwarded by the ASM. The EDMF is acceptable.

Control of Drug Substance
An appropriate specification has been provided for the active substance.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analytical data, which comply with the proposed specification, have been provided.

II.3 Medicinal Product

Excipeints: Mannitol, Cellulose, microcrystalline, Copovidone, Sodium starch glycollate (Type A), Silica, colloidal anhydrous, Magnesium stearate, Hypromellose 5 cps, Talc (micronised), Titanium dioxide (E171), 30 mg tablets: Ferric oxide (E172), Indigotine (E132).

The choice and function of the excipients in the formulation has been described. Compatibility with regard to excipients has been justified by stability results.

All excipients comply with the Ph.Eur. except the colorant Iron oxide red, which complies with NF and the requirements stated in Commission Directive 95/45/EC.

Certificates of analysis for each excipient have been included in the file.

Manufacture
The validation results show that the manufacturing process of Paroxetine is suitable to produce tablets within the specification.

All analytical procedures used for testing the drug product have been properly described.

Finished product specification
The finished product specification has been justified according to relevant EU/ICH Q6A Guideline *Specifications: Test procedures and acceptance criteria for new drug substances and new drug products* and Ph. Eur.

For each strength, results from two batches have been enclosed. The results comply with the proposed specification and the specification limits are considered acceptable compared with the actual results.

During the national approval phase, it has been confirmed by the company, that batch analysis on batches covering the maximum applied batch sizes will be forwarded when available.

Stability
The data supports the shelf life claimed in the SPC:
18 months for the 10 mg strength and 36 months for the 30 mg strength at the storage condition: Do not store above 30°C.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-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 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
Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases with higher single doses or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non-linear kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.
Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy.

Distribution
Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma.
Approximately 95% of the paroxetine present is protein bound at therapeutic concentrations.
No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).
Transfer to human breast milk, and to the foetuses of laboratory animals, occurs in small amounts.

Metabolism
The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.

Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake.

Elimination
Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism.
Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine.
The elimination half-life is variable but is generally about 1 day.

IV.3 Discussion on the clinical aspects

No bioavailability studies have been performed for Paroxetine 10 mg and 30 mg tablets. But the applicant refers to the bioavailability studies performed between Paroxetine® 20 mg and 40 mg film-coated tablets (old formulation), HEXAL and the reference product Seroxat® 20 mg and 40 mg film-coated tablets, GlaxoSmithKline as the granules of paroxetine 10 mg and 30 mg film-coated tablets, HEXAL in composition are identical to the 20 mg and 40 mg film-coated tablets.

At the time of submission of a Type I variation for the new formulation of 20 mg and 40 mg tablets (minor change in composition), the Applicant justified not to submit the new bioavailability studies.
In Module 5.2 it is argued according to section 5.4 in the EU Guideline Investigation of Bioavailability and Bioequivalence not to conduct a bioequivalence study for the 10 mg and 30 mg dosage strengths.
All tablet strengths are manufactured by the same manufacturer and process.
In vitro dissolution tests show that the dissolution profiles of the four strengths of the HEXAL product are similar.
Paroxetine is a highly soluble and highly permeable drug, classified as a Class I drug (Biopharmaceutical Classification System), which indicates that paroxetine is a good candidate for waiver of bioequivalence studies.
It is acceptable that a new bioequivalence study has not been performed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and approval of Paroxetin "Hexal", film-coated tablets is recommended.

V.1 Outstanding issues

The company has made the following commitments:

- Certificate of analysis, including microbiological purity, of the first three production size batches (both strengths) will be forwarded when available.
- Breakability testing will be performed at the end of shelf-life