

# **Public Assessment Report**

## **Scientific discussion**

### **Paroxetin “Aurobindo” Paroxetine**

**DK/H/1135/001-002/DC**

**This module reflects the scientific discussion for the approval of Paroxetin “Aurobindo”. The procedure was finalised at 20-01-2008. For information on changes after this date please refer to the module ‘Update’.**

## I. INTRODUCTION

This assessment report concerns Paroxetin “Aurobindo”, film-coated tablets 20 mg and 30 mg, approved in a Decentralised Procedure on 20<sup>th</sup> January 2008.

The Reference Number for the Decentralised Procedure is DK/H/1135/001-002/DC.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Paroxetine “Aurobindo”, in the treatment of major depressive episodes, obsessive compulsive disorders (OCD), panic disorder with and without agoraphobia, Social anxiety disorders/Social phobia, Generalised Anxiety Disorder and Post-traumatic stress disorder, could be approved.

The application for Paroxetine “Aurobindo” 20 mg and 30 mg film-coated tablets is an abridged generic application made according to Article 10 of Directive 2001/83/EC submitted within the decentralised procedure with Denmark acting as reference member state (RMS). And AT, BE, CY, CZ, DE, EE, EL, ES, FI, HU, IE, LT, LV, NL, NO, PL, PT, SE, SI, SK, UK.

Paroxetin 20 mg is authorised in all CMS and the application is made according to Article(1), Paroxetine 30 mg is not authorised in all CMS, hence;

Paroxetine 30 mg is made according to Article 10(1) in: BE, CY, CZ, EE, EL, HU, IE, LT, LV, NL, PL, SI, SK and UK.

Paroxetine 30 mg is made according to Article 10(3) in: AT, DE, ES, FI, NO,PT and SE.

Essential similarity to the nationally authorised reference innovator product Seroxat 20 mg and 30 mg, marketed by GlaxoSmithKline is claimed. The medicinal product used for the bioequivalence study is Seroxat 30 mg film-coated tablets, marketed by GlaxoSmithKline and purchased from the UK market. Based on this bio-equivalence study results, a waiver for the bio-equivalence study for the 20 mg strength was conducted.

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:** Tablets, film coated.

**Active substance:** Paroxetine hydrochloride hemihydrate.

**Strength:** 20 mg and 30 mg paroxetine.

**Excipients:** Calcium hydrogen phosphate, dihydrate, Lactose monohydrate, Sodium starch glycolate (Type A), Calcium hydrogen phosphate, anhydrous, Magnesium stearate.

20 mg tablets: Opadry white.

30 mg tablets: Opadry blue.

**Shelf life:** 24months.

**Special precautions for storage:** This medicinal product does not require any special storage conditions.

**Nature and content of container:** PVC/PE/PVDC/Aluminium blister packs. Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 60, 98, 100 and 250 film-coated tablets.

## **II.2 2.2 Drug Substance**

**Active substance:** Paroxetine hydrochloride hemihydrate. A monograph for the drug substance paroxetine hydrochloride hemihydrate is presented in Ph. Eur.

The synthesis of the drug substance has been adequately described in the restricted part of the DMF. The control tests and specifications for drug substance are adequately drawn up in line with the Ph. Eur. monograph.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

### **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**

The development of the product has been described, the choice of excipients is justified and their functions explained. The method for dissolution testing has been chosen to be in line with the BP monograph method for paroxetine tablets and has been justified during studies in different dissolution media.

The manufacturing process of the film coated tablets is a standard wet granulation process. It has been sufficiently validated.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 2 batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

### **Stability**

The data supports the shelf-life claimed in the SPC: 2 years with no special storage conditions for the drug product.

### **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**

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 two dosage strengths, i.e. 20 mg and 30 mg. A waiver for bioequivalence study on the 20 mg tablets is requested. This is considered acceptable as all the requirements in the BA-BE guideline is fulfilled: The two strengths are manufactured by the same manufacturer, the qualitative composition is the same with the exception of the colouring agents and the ratio of amount of active substance and excipients are the same. Moreover, the dissolution profiles of the two strengths are similar in different media. The kinetics of paroxetine is non-linear; however, the non-linearity of paroxetine is small and is generally confined to those subjects who achieve low plasma levels at low doses. The non-linearity is due to the partial saturation of the first pass metabolism effect and reduced plasma clearance resulting in disproportionate increases in plasma concentrations of paroxetine with higher single doses. In such a case the highest strength is the most sensitive to identify differences.

#### **Study design**

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 15 days between the two administrations. 30 mg was administered in each period.

The study has been carried out in accordance with GCP, GLP, EMEA guidance and the Declaration of Helsinki.

The design of the study as a single dose study under fasting conditions are considered justified. Although a recommendation is given in the SPC to administer the drug with food it is acceptable that a study under fasting conditions have been carried out, since food does not influence the absorption or bioavailability of paroxetine.

Based on the elimination of the drug substance the sampling period is considered adequate to estimate the pharmacokinetic parameters and the wash-out period is long enough to avoid any carry over effect.

Populations studied:

28+2 healthy Indian male subjects (19-42 years) participated in the study. 26 subjects completed both periods of the study and were used for pharmacokinetic and statistical analysis.

Based on the submitted bioequivalence study Paroxetine Aurobindo film coated tablets is considered bioequivalent with Seroxat film coated tablets, GlaxoSmithkline.

## V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and approval of Paroxetine “Aurobindo”, film-coated tablets is recommended.

### V.1 Outstanding issues

#### Commitments

- The updated specification with version number and method references will be provided when the specification are agreed by all CMSs, i.e. by the end of the DCP procedure. (**Fulfilled 26-06-2008**).
- Process validation will be performed on the first 3 batches of the maximum production batch size, (of each strength) manufactured at proposed manufacturing site and the results provided, when available.
- Certificates of analysis performed on the first 3 consecutive production scale batches (of each strength) will be forwarded when available.
- The enclosed stability studies will be continued.
- The first 3 production batches of each strength will be put on stability and tested according to the stability protocol.