

Public Assessment Report

Scientific discussion

**Paroxetine Jubilant 10 mg, 20 mg, 30 mg
and 40 mg film-coated tablets**

(paroxetine)

NL/H/3147/001-004/DC

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This module reflects the scientific discussion for the approval of Paroxetine Jubilant 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets. The procedure was finalised on 29 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paroxetine Jubilant 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets from Jubilant Pharmaceuticals N.V.

The product is indicated for treatment of:

- Major Depressive Episode
- Obsessive Compulsive Disorder
- Panic Disorder with and without agoraphobia
- Social Anxiety Disorders/Social phobia
- Generalised Anxiety Disorder
- Post-traumatic Stress Disorder

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Seroxat 10 mg, 20 mg and 30 mg, film-coated tablets (NL License RVG 29433, 14668, 27135) which have been registered in the Netherlands by GlaxoSmithKline B.V. since 2004, 1991 and 2001 respectively. The innovator product is not available as a 40 mg tablet. However, considering that 40 mg is within the recommended dosing range in the posology, the Paroxetine Jubilant 40 mg tablet is considered acceptable.

The concerned member states (CMS) involved in this procedure were Cyprus and the United Kingdom.

The marketing authorisation for the 10 mg, 20 mg and 30 mg strengths has been granted pursuant to Article 10(1) of Directive 2001/83/EC. For the 40 mg the legal base is 10(3) – hybrid application, in view of the difference in strength from the innovator.

II. QUALITY ASPECTS

II.1 Introduction

Paroxetine Jubilant film-coated tablets contain 10 mg/20 mg/30 mg/40 mg paroxetine (as paroxetine hydrochloride hemihydrate).

Paroxetine Jubilant 10 mg is a white, modified capsule shaped, film-coated tablet, scored on one side and debossed with '457' on the other side.

Paroxetine Jubilant 20 mg is a white, modified capsule shaped, film-coated tablet, scored on one side and debossed with '458' on the other side. The tablet can be divided into equal doses.

Paroxetine Jubilant 30 mg is a blue, modified capsule shaped, film-coated tablet, scored on one side and debossed with '459' on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Paroxetine Jubilant 40 mg is a white, modified capsule shaped, film-coated tablet, scored on one side and debossed with '460' on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in blister packs comprising white opaque PVC film backed with aluminium foil.

The excipients are:

Tablet core - calcium hydrogen phosphate dihydrate (E341), pregelatinized starch, sodium starch glycolate (Type A), magnesium stearate (E470b)

Tablet coating - hypromellose (E464), titanium dioxide (E171), macrogol 400, polysorbate 80 (E433), Indigo Carmine Aluminium lake (E132) (30 mg only)

The different strengths are fully dose proportional.

II.2 Drug Substance

Paroxetine hydrochloride hemihydrate is a well known active substance, described in the European Pharmacopeia. The substance is non-hygroscopic. Paroxetine hydrochloride hemihydrate is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol 96% and in methylene chloride. Further, the substance shows polymorphism. The hemihydrate polymorphic form is manufactured. Consistent and stable polymorphic form of the drug substance has been sufficiently justified.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents and particle size. The specification is acceptable.

Batch analysis data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance

The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During the development studies such as characterization of reference products, in-vitro dissolution of originator film-coated tablets, breakability of tablets and investigations of manufacturing process parameters were performed. The choice of the packaging is justified.

The breakability test has been performed in line with the requirements in the Ph.Eur. (subdivision of tablets), with one batch per strength for the 10 and 20 mg. The tablets conform with the test. The score line on the 30 and 40 mg tablet is not intended for division into equal doses.

The bioequivalence study test batch was manufactured according to the finalized manufacturing process and composition, and the provided comparative dissolution profiles in support of the bioequivalence study are acceptable.

Manufacturing process

The manufacturing process of paroxetine film-coated tablets involves dispensing of raw materials, sifting, dry mixing, granulation, drying, milling, blending of granules, lubrication, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for two pilot batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients comply with the Ph.Eur., except for the Opadry coating materials, for which in-house specifications are applied. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, dimensions, identity (of the active substance as well as colorants), loss on drying, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The release and shelf-life requirements/limits are identical, except regarding loss on drying (shelf-life limits are wider than release limits). The specification and limits are acceptable. Batch analysis data from the proposed production site have been provided for two pilot batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data of the product have been provided for two pilot batches per strength stored at 25°C/60% RH (12 and 18 months) and 40°C/75% RH (6 months) in the packaging material intended for marketing, i.e. blister packs comprising white opaque PVC film backed with aluminium foil. The conditions used in the stability studies are according to the ICH stability guideline. The product remains stable throughout the tested period, at long term and accelerated conditions. It has been demonstrated that the product is insensitive to light exposure.

Based on the results in the stability studies provided up to date, the storage conditions in the shelf-life "two years, no special storage conditions" in the proposed blister is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Paroxetine Jubilant has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paroxetine Jubilant is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Seroxat, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Paroxetine Jubilant 40 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of two tablets of the reference product Seroxat 20 mg film-coated tablets (GlaxoSmithKline UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

All four tablet strengths are manufactured by the same manufacturing process, their quantitative composition is the same and their composition is quantitatively proportional. Comparative dissolution testing was performed according to the guideline requirements. Similarity between the 40 mg test biobatch and the additional 10, 20 and 30 mg is demonstrated at pH 1.2 and 4.5 (>85% was dissolved in 15 min). At pH 6.8, similarity was shown between the 40 mg biobatch and 30 mg tablet. Similarity in the dissolution at pH 6.8 for the 10 and 20 mg with the 40 mg biobatch was not shown. The MAH performed dissolution at the same dose: 40 mg vs 4x10 mg and 40 mg vs 2x20 mg, where the similarity could be shown. These results point to the solubility limitations rather than to a formulation effect. In conclusion, the biowaiver for the 10, 20 and 30 mg tablets is considered to be sufficiently justified and can be granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-42 years. Each subject received a single dose (40 mg or 2 x 20 mg) of one of the 2 paroxetine formulations. The tablets were orally administered with 240 ml water after an overnight fast of 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 1.00, 2.00, 3.00, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.33, 6.67, 7.00, 7.33, 7.67, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The sampling schedule is considered sufficiently rich around expected t_{max} of 5-8 hours to adequately determine C_{max} . Considering $t_{1/2}$ of approximately one day, the sampling duration up to 72 hours and the wash-out period of 15 days are sufficient long to adequately cover the absorption phase and to avoid the carry-over effect, respectively.

It is known from the literature that food does not affect significantly the absorption of paroxetine and the innovator product, Seroxat, is recommended to be taken with food not to enhance the bioavailability but most probably to improve gastro-intestinal tolerability. Therefore, fasting conditions are considered acceptable to investigate bioequivalence of a generic paroxetine formulation.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects were withdrawn from the study and one dropped out. One subject was withdrawn in Period I, and a second subject was withdrawn in Period II, both due to an adverse event (vomiting). One subject dropped out of the study in Period I due to personal reasons. Twenty-seven subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ (median, range)) of paroxetine under fasted conditions.

Treatment N=27	AUC ₀₋₇₂ ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	866.07 $\pm$ 619	NA	40.81 $\pm$ 18	5 (4.33-7)	--
Reference	824.12 $\pm$ 569	NA	39.31 $\pm$ 17	5 (4.33-8)	--
*Ratio (90% CI)	1.05 (0.97 – 1.13)	NA	1.03 (0.93 -1.13)	--	--
CV (%)	--	--	--	--	--
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC ₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C _{max} maximum plasma concentration t _{max} time for maximum concentration t _{1/2} half-life CV coefficient of variation					

*In-transformed values

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Paroxetine Jubilant 40 mg is considered bioequivalent with two Seroxat 20 mg film-coated tablets.

A total of four adverse events were recorded in the study, which were assessed as mild and moderate in severity having possible relationship to study drug: vomiting (2x), headache and loose motion. There was no serious adverse event recorded in the study.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Paroxetine Jubilant.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Serotonin syndrome and drug interactions with serotonergic medicines including MAO inhibitors - Risk of suicidal behavior - Risk of withdrawal reactions
Important potential risks	- Aggravation/precipitation of epilepsy or seizures - Increased risk of bone fractures - Risk of haemorrhage - Altered glycemic control in diabetic patients
Missing information	- Off-label use - Use in pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Seroxat. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The type of test used for the readability testing of this PL was an evaluation and problem-seeking test.

All participants were able to trace the information for the questions 95% of the time. Each of the participants showed they understood the information by answering the questions correctly more than 95% of the time. There were no revisions suggested to the PL, which is considered acceptable. User testing is considered to have been carried out successfully

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paroxetine Jubilant 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroxat. Seroxat is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paroxetine Jubilant with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 May 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update of the SmPC and PL to be fully compliant with the innovator.	NL/H/3147/001-004/IB/001	IB	9-2-2016	10-3-2016	Approved	N