CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paroxetine 10, 20, 30 and 40 mg tablets I.C.C. B.V., the Netherlands

paroxetine hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/831/001-004/MR
Registration number in the Netherlands: RVG 33145-8,

23 June 2009

Pharmacotherapeutic group:	antidepressant, selective serotonin reuptake inhibitors
ATC code:	N06AB05
Route of administration:	oral
Therapeutic indication:	major depressive episode, obsessive compulsive disorder, panic disorder, social anxiety disorders, generalised anxiety disorder, post-traumatic stress disorder
Prescription status:	prescription only
Date of first authorisation in NL:	20 December 2005
Concerned Member States:	Mutual recognition procedure with BE, CY, DE, EL, ES, FR, IT, LU, and PT.
Application type/legal basis:	Directive 2001/83/EC, Articles 10(1) and 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Paroxetine 10, 20, 30, and 40 mg, from I.C.C. B.V. The date of authorization was on 20 December 2005 in the Netherlands. The product is indicated for the 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 SPC.

Paroxetine is a potent and selective inhibitor of 5–hydroxytryptamine (5–HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of OCD, Social Anxiety Disorder / Social Phobia, General Anxiety Disorder, Post–traumatic Stress Disorder and Panic Disorder is thought to be related to its specific inhibition of 5–HT uptake in brain neurones.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Seroxat 10, 20 and 30 mg tablets (NL RVG 29433, 14668, 27135) which have been registered in the Netherlands by GlaxoSmithKline B.V. since 2004, 1991, and 2001 respectively (original product). In addition, reference is made to Seroxat and Deroxat authorisations in the individual member states (reference product).

Legal basis
As far as the 10, 20 and 30 mg formulation are concerned, the legal base for Marketing Authorisation in The Netherlands is according to EEC-Directive 2001/83/EC, article 10(1) – generic application.
In part of the CMSs the legal basis of the application for Paroxetine 10 mg, tablets and Paroxetine 30 mg, tablets will be according to EEC-Directive 2001/83/EC, article 10(3) – hybrid application. These deviations are made owing to the absence of these strengths for the innovator in the CMS involved. However, since the strengths applied for are in agreement with the posology this is deemed acceptable.

In the Netherlands, Paroxetine 40 mg, tablets have been registered following the abridged procedure according to EEC-Directive 2001/83/EC, article 10(3) – hybrid application, owing to the absence of this strength for the innovator. The same legal base will be applicable in the CMSs. Since the strength applied for is in agreement with the posology, this is deemed acceptable.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Deroxat 20 mg, registered in France, and Seroxat 20 mg, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is paroxetine hydrochloride (HCl) anhydrous, an established active substance substance described in the European Pharmacopoeia (Ph.Eur.*). Paroxetine HCl is a white to off-white, crystalline, hygroscopic powder. It is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and in methylene chloride. It shows polymorphism.
Paroxetine has two chiral centres. As a consequence there are theoretically 4 stereoisomers: trans(+/-) and cis(+/-). The active configuration is the trans(-) configuration. Both cis isomers and the trans(+) isomer are limited as impurities by the HPLC-methods described in the EP monograph. The enantiomeric purity of the active substance is fully controlled by the stated specifications and analytical methods applied by the DMF-holder.
Several polymorphic forms of paroxetine hydrochloride exist: hemihydrate anhydrate form A, polymorph B, and polymorph C. The active substance is the anhydrate form A.

Manufacture
The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

A flow chart of the synthesisand a detailed description has been included. A list of all starting materials and reagents is included. For all these materials specifications are submitted. All specifications are acceptable. The manufacturing process has been adequately described.

Specification
The active substance specification is considered adequate to control the quality and meets the requirements of the DMF holder and the specific monograph in the Ph.Eur. Where difference exists, the DMF specifications are tighter. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches.

Stability
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines. Stability data for 36 months for 1 batch and 24 months at 25ºC/60%RH were available, as well as 24 months for 2 batches at 30ºC/70%RH and 3 batches at 40ºC/75% RH for 6 months. Based on the data submitted, a retest period could be granted of 2 years when stored in a tight container at NMT 25ºC, protected from light, in double inner bags of PE and an aluminium bag coated with PE.

Discussion stability results
There was no significant change of the tested parameters, except for water content, melting point, and DSC. Due to the pronounced hygroscopicity the water content may increase rapidly. Although the amount of water increases no significant changes in impurities and assay can be seen in the stability data. Therefore, it is not expected that the amount of water has any influence on the stability of the active substance. Furthermore, only one data point was out of specification. Therefore, this out of specification result is no objection.
At timepoints 3 and/or 6 months for two batches the DSC shows a secondary peak at 40°C/75% RH.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Paroxetine 10, 20, 30, and 40 mg tablets contain as active substance 11.1, 22.2, 33.3, and 44.4 mg of paroxetine hydrochloride respectively, and are

10 mg: biconvex off white round tablets inscribed 10 on one side.
20 mg: flat faced bevel edged off white round tablets inscribed 20 on one side with a score line. The tablets can be divided into equal halves.
30 mg: flat faced bevel edged off white round tablets with a score line. The tablets can be divided into equal halves.
40 mg: capsule shaped off white tablets with a score line. The tablets can be divided into equal halves.

The tablets are packed in polyvinylchloride foil – aluminium foil blisters.

The excipients are: cellulose microcrystalline (E 460), calcium hydrogen phosphate dihydrate (E 341), croscarmellose sodium (E 468), silica colloidal anhydrous (E 551), magnesium stearate (E 470b).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The formulation is an immediate release, dispersible tablet. The strengths are completely dose proportional. Development was performed in order to obtain a suitable tablet for immediate release with a simple manufacturing method. Disintegration should be quick, dissolution >85% after 15 minutes, uniformity of content complying and breakability within requirements of the EP.

Excipients
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs. For microcrystalline cellulose, calcium hydrogen sulphate, and, croscarmellose sodium an additional specification for particle size is set.

Dissolution profiles
Dissolution is compared for the 20 mg biobatch in 3 different media, with the FR reference product, and innovator products from NL, DE, SE, DK, NO, FI, EL, IT, ES, BE, PT, RO, SK, CZ and LT. The 30 mg strength was compared with the innovator products from SK and CZ in 3 different media. Dissolution profiles were provided of the 10 and 40 mg strengths in 3 different media.
The dissolution of the 4 strengths are all above 85% in 15 minutes. Therefore, the dissolution profile of the 4 strenghts is comparable.
The dissolution profile of the German and French innovator products are comparable with the dissolution profile of the Dutch innovator and of the proposed product.

Batches used in the bioequivalence studies
20 mg: The formula of this batch is identical to the formula proposed for marketing. The batch size represented 4% of the production batch size. However, at the time of registration in the RMS it was 10% of production size. From the process validation data it appeared that upscaling had no influence on the quality of the finished product. Therefore, from a chemical-pharmaceutical point of view it is acceptable that the batch size of the biobatch was not pilot-scale according to the definition in the *Note for Guidance on Investigation of bioavailability and bioequivalence*.
40 mg: The batch size of biobatch is acceptable in view of the maximum batch size for the 40 mg strength (30%).

Manufacturing process
For each strength a flow chart is enclosed. The manufacturing follows the steps of sieving and weighing the raw materials. After each addition the mixture is mixed. Finally, the mixture is compressed into tablets. Information on mixing speeds and apparatus have been included in the dossier.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches of the 10, 30, and 40 mg strength, and for 8 batches of the 20 mg strength in accordance with the relevant European guidelines.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for general description, diameter, thickness, length, width, average weight, uniformity of weight, disintegration, fineness of dispersion, tablet hardness, breakability, identification, assay, content uniformity, related substances, dissolution, and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Pharmacopoeial requirements are met.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 3 batches of the 10, 30, and 40 mg strengths and 9 batches of the 20 mg strength have been provided from the proposed production site(s), demonstrating compliance with the specification.

Breakability:
The requirements for the halved tablets are in accordance with the EP uniformity of mass. The MAH has committed to provide breakability results at the end of shelf life (36 months) in respect of remaining 20 mg stability batches, and 30 mg and 40 mg stability batches, to RMS and CMS's.

Container Closure System
Blisters and PP bottles are used. The tablets were packed in opaque PVC and thicker aluminum foil.

Stability tests on the finished product
Stability data on the 10 mg, 30 mg and 40 mg strengths have been provided for 3 batches each, stored at 25ºC/60%RH. For the 20 mg strength stability data have been provided for 5 batches. These 20 mg batches have been stored at 25ºC/60%RH and 40ºC/75%RH. On basis of the data submitted, a shelf life was granted of 3 years, without specific storage conditions.

The MAH has committed to place the first three commercial batches of 10 mg, 30 mg, and 40 mg tablets on stability (accelerated and real time), and thereafter to place a single strength, on a cyclical basis, on rolling stability for all four strengths.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Seroxat, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of paroxetine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted 2 bioequivalence studies. ICC B.V. has first registered the 20 mg paroxetine tablets in the Netherlands, for which a bioequivalence study was submitted comparing the 20 mg paroxetine tablet with the French reference product Deroxat 20 mg. For the application for marketing authorisation of the 10, 30 and 40 mg formulation a second bioequivalence study was submitted, comparing the 40 mg paroxetine tablet with two doses of the German reference product Seroxat 20 mg tablets.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

Bioequivalence study: 20 mg Paroxetine tablets

Test : Paroxetine, 20 mg tablet (I.C.C. B.V., the Netherlands).
Reference : Deroxat 20 mg (SmithKline-Beecham, France).

A comparative open, crossover bioequivalence study was carried out under fasted conditions in 32 healthy volunteers. No demographic data were submitted of these volunteers. Each subject received a single dose (20 mg) of one of the 2 paroxetine formulations. The tablet was orally administered with 150 ml water after a 10 h fasting period. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 12, 24, 36, and 48 hours after administration of the products. All 32 subjects were eligible for pharmacokinetic analysis.

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

A large inter-individual coefficient of variation is observed in the pharmacokinetic variables as could be expected, due to the involvement of polymorphism of the metabolising enzyme 2D6. Subjects were not selected for poor or extensive metabolisers. In addition, some subjects had already values below the LLQ at 12 hours after administration of the products. Extrapolation to infinity was than based upon the last measurable values, resulting in an overestimation of the $AUC_{0-\infty}$. The extrapolated part of the AUC was in several cases more (even up to 3-fold) than AUC_{0-t}.

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

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	102 ± 138	189 ± 265	5.7 ± 4.2	5.0 (3.0 – 7.5)	18 ± 11
Reference	100 ± 127	162 ± 200	5.5 ± 3.9	5.5 (3.5 – 7.5)	17 ± 12
***Ratio (90% CI)**	0.97 (0.83 – 1.13)	1.12 (0.98 – 1.27)	1.04 (0.93 – 1.15)	---	---
CV (%)	36.6	30.6	24.8	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Based on the pharmacokinetic parameters of paroxetine, the French reference Deroxat 20 mg tablet and test Paroxetine 20 mg tablet are bioequivalent with respect to the rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.
With regard to $AUC_{0-\infty}$ no equivalence could be proven. The 90% confidence interval was just outside the acceptance range. However, $AUC_{0-\infty}$ was not correctly calculated, leading to an overestimation of the AUC. In an additional submitted report, $AUC_{0-\infty}$ was calculated by taking into account the LLQ plasma values (thus when the LLQ was already reached within 48 hours after administration of the products, the plasma levels were set to zero). In this case $AUC_{0-\infty}$ is matching AUC_{0-t}. Using these corrected data, the 90% confidence interval calculated for $AUC_{0-\infty}$ is also within the acceptance range of 0.80 – 1.25. This approach was agreed. In addition, this positive conclusion was confirmed by a second bio-equivalence study (see below).

Bioequivalence study 2: 40 mg Paroxetine tablets

Test : Paroxetine, 40 mg tablet (I.C.C. B.V. the Netherlands).
Reference : Seroxat 20 mg (SmithKline-Beecham, Germany).

A two-period two-sequence, cross-over controlled, block randomised, single-dose bioequivalence study was carried out under fasted conditions in 48 healthy volunteers (21 males and 27 females) aged 18 to 45 years. Subjects were CYP2D6 extensive metabolisers as assessed by dextromethorphan phenotype test. Each subject received a single dose (40 mg; one test tablet of 40 mg or 2x 20 mg of reference tablet) of one of the 2 paroxetine formulations. The tablet was orally administered with 200 ml water after a 10 h fasting period. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after administration of the products. Six subjects dropped out: 4 subjects by their own decision, 1 subject was withdrawn because of the intake of concomitant medication and 1 subject because of a positive pregnancy test. Fourty-two subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of paroxetine under fasted conditions.

Treatment N=42	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	355 ± 248	364 ± 262	15.5 ± 7.1	4.0 (2.0 – 7.0)	15 ± 8
Reference	391 ± 255	403 ± 272	16.8 ± 7.1	4.5 (3.0 – 8.0)	15 ± 9
***Ratio (90% CI)**	0.89 (0.84 – 0.94)	0.89 (0.84 – 0.93)	0.91 (0.85 – 0.96)	---	---
CV (%)	13.4	13.1	16.0	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Based on the pharmacokinetic parameters of paroxetine, the German reference Seroxat 2 x 20 mg tablet and test Paroxetine 40 mg tablet are bioequivalent with respect to the rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The 90% confidence intervals calculated for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25, and comparable to those calculated by the MAH.

The 10, 20, 30 and 40 mg tablets are dose proportional. Furthermore, the tablets were manufactured by the same manufacturer and process, have comparable dissolution profiles and have more or less linear pharmacokinetics. Therefore, the results obtained in the bioequivalence study can be extrapolated to the 10 and 30 mg tablets.

The MEB has been assured that the bioequivalence studies have 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).

During the procedure, two CMSs raised public health objections to the bioequivalence study with the 40 mg strength. The size of biobatch was not in accordance with the Note for Guidance published in 2001, while the biobatch was produced in 2002. The *a posteriori* justification for deviation to the minimum requirements was not considered acceptable by these CMS's. Therefore, a referral to the CMD(h) was started.

In the CMD(h) meeting of 12 December 2006, the following was discussed:
It was acknowledged, that there was a deviation of the guidelines. However, according to the RMS, the MAH has adequately argued that the biobatches are representative for the product on full production scale and it is not expected that the bioavailability of the biobatch will differ from a batch of tablets that would have been produced from the full amount of bulk blend.
Nevertheless, to finalize the procedure and not to deviate from generally accepted standards, the MAH committed to perform a new BE in line with the European guidelines and to report on the results within 6 months.
Agreement reached with a commitment of the MAH. The MAH committed to perform a new Bioequivalence study with a batch of the 40 mg strengh, fulfilling the minimum requirements on the biobatch, as mentioned in the NfG. This commitment has been fulfilled. See annex I,

Risk management plan

Paroxetine was first approved in 1990 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of paroxetine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The proposed SPC is based on the SPC as issued by the European Commission on 29 March 2005. As compared to the latter version, the SPC has been amended to take into account any subsequent relevant and finalized Type II variation for the innovator product, i.e. Seroxat (NL/H/566-570, 591-2). In addition, the wording in section 4.4 regarding use in children and adolescents under 18 years of age has been updated in line with the Commission Decision, issued on 19 August 2005.

Hence, the proposed SPC is in accordance with relevant Commission Decisions regarding paroxetine-containing products, and, except for product-specific information, such as product names, marketing authorisation holder, excipients and packaging, the SPC is identical to the current harmonized SPC for the innovator product Seroxat.

Readability test

A readability test has been performed in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was diagnostic and scoring. This is acceptable because several questions were posed to identify potential points that showed room for improvement of the PIL in terms of traceability, comprehensibility and usability. The PIL readability testing was performed in two phases. Two test rounds were performed with 10 test persons in each test round.

Based upon the results, it can be concluded that the traceability, comprehensibility and usability of the information in the leaflet can be considered sufficient, although on one specific item the score remained below 80% after the second round.

With regard to the non-specific open questions, it should be noted that the leaflet scored well in terms of completeness and functionality, but less in terms of “tempting to read” and conciseness. It is recognized that a leaflet that meets the requirements for completeness and functionality may appear less attractive and concise to the patient. Since the SPC for paroxetine-containing products is extensive and because from a regulatory point of view all relevant information should be included in the patient leaflet, the lesser score for “tempting to read” and conciseness is deemed acceptable.

A few changes have been introduced in the patient information leaflet as compared to the tested version. First, the patient information leaflet has been amended in accordance with the current version of the QRD-template for MR/DC procedures. Second, in accordance with the innovator’s product information, the following items have been introduced and/or have been updated: concomitant use with pimozide as a contra-indication, interaction with atomoxetine, potential risk of malformation during pregnancy, frequency of occurrence of agitation. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paroxetine 10, 20, 30, and 40 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Seroxat tablets. 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, see also below the discussion in the CMD(h) meeting.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

A specific Risk Management Plan is not deemed necessary, since paroxetine is a well-known substance. Since the products at issue are intended for generic substitution, no additional safety issues are identified.

The proposed SPC is in accordance with relevant Commission Decisions regarding paroxetine-containing products, and, except for product-specific information, such as product names, marketing authorisation holder, excipients and packaging, the SPC is identical to the current harmonized SPC for the innovator product Seroxat. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Paroxetine 10, 20, 30, and 40 mg tablets were authorised in the Netherlands on 20 December 2005.

During the procedure, two CMSs raised public health objections to the bioequivalence study with the 40 mg strength. The size of biobatch (5.000 units / 40 mg strength) is not in accordance with the Note for Guidance published in 2001, while the biobatch was produced in 2002. The *a posteriori* justification for deviation to the minimum requirements was not considered acceptable by these CMS's. Therefore, a referral to the CMD(h) was started.

Following the discussion in the CMD(h) meeting of 12 December 2006, agreement reached with a commitment of the MAH. The MAH committed to perform a new Bioequivalence study with a batch of the 40 mg strengh, fulfilling the minimum requirements on the biobatch, as mentioned in the NfG. This commitment has been fulfilled (see Annex I).

The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paroxetine 10/20/30/40 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 December 2006.

The PSUR-cycle will be according to the current legislation and in line with the paroxetine article 31 referral. PSURs will be submitted every 6 months for the first two years. The first PSUR will cover the period from October 2006 to April 2007.

The date for the first renewal will be: 4 October 2011.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH has committed to place the first three commercial batches of 10 mg, 30 mg, and 40 mg tablets on stability (accelerated and real time), and thereafter to place a single strength, on a cyclical basis, on rolling stability for all four strengths.
- The MAH has committed to provide breakability results at the end of shelf life (36 months) in respect of remaining 20 mg stability batches, and 30 mg and 40 mg stability batches, to RMS and CMS's.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NfG	Note for Guidance
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Change in the pack size of the finished product. Adding boxes containing 20, 50 and 100 tablets.	NL/H/0831/ 001&004 /IA/001	IA	19-3-2007	2-4-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0831/ 001&004 /IA/002	IA	19-3-2007	2-4-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0831/ 001&004 /IA/003	IA	19-3-2007	2-4-2007	Approval	N
Change to batch release arrangements and quality control testing of the finshed product. Replacement or addition of a manufacturer responsbile for batch release, not including batch control/testing.	NL/H/0831/ 001&004 /IA/004	IA	19-3-2007	2-4-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0831/ 001-004 /IA/005	IA	15-8-2007	29-8-2007	Approval	N
Change to batch release arrangements and quality control testing of the finshed product. Replacement or addition of a manufacturer responsbile for batch release, not including batch control/testing.	NL/H/0831/ 001-004 /IA/006	IA	15-8-2007	29-8-2007	Approval	N
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a new manufacturer (replacement or addition). Other substances.	NL/H/0831/ 001-004 /IA/007	IA	11-12-2007	25-12-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0831/ 001-004 /IA/008	IA	15-8-2007	29-8-2007	Approval	N
Change to batch release arrangements and quality control testing of the finshed product. Replacement or addition of a manufacturer responsbile for batch release, not including batch control/testing.	NL/H/0831/ 001-004 /IA/009	IA	15-8-2007	29-8-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets	NL/H/0831/ 001-004 /IA/010	IA	11-12-2007	25-12-2007	Approval	N

and capsules.						
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0831/ 001-004 /IA/011	IA	11-12-2007	25-12-2007	Approval	N
Type II amendements of SPC and PIL for antidepressants.	NL/H/0831/ 001-004 /II/012	II	28-3-2008	10-4-2008	Approval	Y, Annex II

Annex I to the PAR

POST-approval Commitment – Bioequivalence study with 40 mg strength

During the MRP, questions were raised regarding the size of the batch of 40 mg tablets used in the bio-equivalence study. The size of biobatch was not in accordance with the Note for Guidance published in 2001, while the biobatch was produced in 2002. The *a posteriori* justification for deviation to the minimum requirements was not considered acceptable by these CMS's. Therefore, a referral was raised in the CMD(h). It was decided that Marketing Authorisation could be approved, provided that the Applicant would fulfil the following post-authorization commitment:

The MAH committed to perform a new Bioequivalence study with a batch of the 40 mg strengh, fulfilling the minimum requirements on the biobatch, as mentioned in the NfG..

In order to fulfil the Post-Authorization Commitment, the Applicant submitted data of one new bioequivalence study where the 40 mg test tablet was compared to a similar dose of the French innovator product.

Bioequivalence study 3: 40 mg Paroxetine tablets

Test : Paroxetine 40 mg tablet (I.C.C.B.v., the Netherlands)
Reference : Deroxat (2 x) 20 mg (SmithKline-Beecham, France).

A two-period, cross-over, block randomized, single dose administration bioequivalence study was carried out under fasted conditions in 42 healthy male volunteers, aged 18 to 45 years. The volunteers were hospitalized until 24 hours post administration. Each subject received a single dose (2 x 20 mg test, 1 x 40 mg reference) of one of the 2 paroxetine formulations. The tablet was orally administered with 240 ml water after a fasting period. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after each administration of the products. One subject was withdrawn from the study because of a positive alcohol test at entrance, and one subject withdrew for personal reasons. Forty subjects were eligible for pharmacokinetic analysis.

In order to prevent high plasma concentrations at the high dose of 40 mg, only volunteers phenotyped as extensive CYP2D6 metabolisers were included.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of paroxetine under fasted conditions.

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	337	349	13	5.426	15.282
Reference	358	373	13	6.150	15.369
***Ratio (90% CI)**	95.9 (89.9 – 102.3)	96.1 (90.1 – 102.4)	95.4 (88.8 – 102.4)	---	---
CV (%)	17.1	16.9	18.9	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of paroxetine under fasted conditions, it can be concluded that test Paroxetine and reference Deroxat tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The batch size is now in accordance with the Note for Guidance published in 2001. The results support the earlier recommendation of the RMS to provide marketing authorisation for the products at issue. The member states considered the post-approval commitment fulfilled.

Annex II to the PAR – Type II variation, amendments of SPC and PIL for antidepressants

PhVWP core SPC wording for all antidepressants

The Pharmacovigilance Working Party has on a number of occasions, examined the possible relationship between suicidal behaviours and the use of Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants.

An Article 31 referral, which concluded in June 2005, resulted in warnings concerning the use of these products in the paediatric population being added to all SPCs for SSRIs and other antidepressants.

The PhVWP considered these texts and concluded that the EU class wording in summaries of product characteristics for SSRIs and other antidepressants which was agreed in 2005 should be updated to more fully reflect current evidence regarding potential risk for suicidal behaviours with antidepressants. The PhVWP also concluded that the agreed class wording should be applied to all antidepressants. Patient information leaflets should be updated to provide more comprehensive and helpful information for patients taking these medicines. The agreed wording for summaries of product characteristics and patient information leaflets is provided below.

SUICIDAL THOUGHTS/BEHAVIOUR

Section 4.4 - Special Warnings and Special Precautions for Use

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Paroxetine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. ***[Please note: This paragraph only needs to be included in the SPCs for medicinal products which have additional indications to a depression indication]***

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Section 4.8
Where reports of suicidal thoughts or behaviour have been reported with a particular product, this should be reflected in section 4.8

Where a table of adverse drug reactions (ADRs) is included in this section, suicidal ideation and suicidal behaviour should be included in this table – frequency not known and include the following as a footnote:

“Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation (see section 4.4).”

Where no table of ADRs is included the above text should be inserted in this section.