CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution
Kiron Pharmaceutica B.V., the Netherlands

paroxetine (as mesylate)

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/877/01/MR
Registration number in the Netherlands: RVG 32691

22 December 2009

Pharmacotherapeutic group:	antidepressant, selective serotonin reuptake inhibitor
ATC code:	N06AB05
Route of administration:	oral
Therapeutic indication:	major depressive episode, obsessive compulsive disorder (OCD), panic disorder with and without agoraphobia, social anxiety disorder / social phobia, generalised anxiety disorder, post-traumatic stress disorder
Prescription status:	prescription only
Date of first authorisation (national):	27 April 2006
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, ES, IT, and UK
Application type/legal basis:	Directive 2001/83/EC article 10(1)

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 Kiron 33.1 mg/ml, drops for oral use, solution, from Kiron Pharmaceutica B.V. The date of authorisation was on 27 April 2006 in the Netherlands. The product is indicated for the treatment of:

- Major depressive episode
- Obsessive compulsive disorder (OCD)
- Panic disorder with and without agoraphobia
- Social anxiety disorder / 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 20 mg tablets (NL license RVG 14668), which has been registered in the Netherlands since 1991 by GlaxoSmithKline B.V.

Legal basis
Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution contains the active substance paroxetine mesilate. The originator product (Seroxat) contains as active substance paroxetine hydrochloride. It has been demonstrated that the different salts do not differ significantly in properties with regard to safety and/or efficacy. The originator product contains 20 mg paroxetine per tablet and the oral drop formulation 20 mg per dosage of 20 drops. Bioequivalence has been proven between Seroxat 20 mg tablets and 'Paroxetine 20 mg (as mesilate)/20 drops, oral drops'.
'Paroxetine 20 mg (as mesilate)/20 drops, oral drops' is an immediate-release oral pharmaceutical form like paroxetine tablets and as such these two formulations shall be considered to be one and the same pharmaceutical form.

Because the product 'Paroxetine 20 mg (as mesilate)/20 drops, oral drops' meets the requirements as laid down in Article 10.1 and 10.2*, a legal base of Article 10(1) generic application is justified."

* *"A 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. ....* ***The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form****. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines."*

Seroxat 20 mg tablets have been registered in the Netherlands by GlaxoSmithKline since 1991. In addition, reference is made to Seroxat and Deroxat 20 mg authorisations in the individual member states (reference product).
In the Netherlands, 2 mg/ml paroxetine containing oral suspensions are registered, both the innovator (Seroxat) and generic products.

Paroxetine Kiron 33.1 mg/ml, drops for oral use, have been registered in accordance with EEC-directive 2001/83/EC, article 10.1 (a) iii, first/second paragraph, corresponding with article 10(1) of the current Directive.

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 applications, 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Seroxat 20 mg tablets, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture has no influence on efficacy and safety. A generic product can be used instead of its 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 (as paroxetine mesylate), an established active substance not described in any Pharmacopoeia. Paroxetine mesylate is a white to almost white powder. It is very soluble in water, soluble in ethanol, sparingly soluble in 2-propanol, ethyl acetate and in acetone. 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 as described in the EP monograph "Paroxetine hydrochloride". The enantiomeric purity of the active substance is fully controlled by the stated specifications and analytical methods applied by the DMF-holder. No polymorphism is observed when paroxetine mesylate is manufactured according to the synthetic route described.

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 MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and 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 use in the medicinal product.

Manufacture
Both AMS's use the same synthetic process, ending in a final purification phase. All reactions and purifications are under adequate control, assuring the exclusion of carreid-over impurities to acceptable levels.

Specification
There are specifications for assay, appearance, pH, specific optical rotation, residue on ignition, identification, related substances, enantiometric purity and water content. Appropriate additional specifications are proposed for residual solvents and particle size. The active substance specification is considered adequate to guarantee a consistent and sufficient quality. All non-compendial methods were validated.

Stability
Stability data on the active substance have been obtained for 4 batches during storage at 25ºC/60%RH (36 months) and 40ºC/60%RH (6 months). There were no significant change of the tested parameters. Based on the stability provided, a retest period of 3 years could be granted without special storage conditions in the tested package.

Medicinal Product

Composition
The product at issue, "Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution", equivalent to 33.1 mg Paroxetine base/ml formulation (i.e. 32.6 mg/g formulation), is a multidose oral solution formulation. The maximum daily dose according to the SPC is 60 mg.
The drops contain 33,1 mg of paroxetine per ml as paroxetine mesylate, whereas the originator product contains paroxetine hydrochloride hemihydrate. The meslyate and hydrochloride salts are considered pharmaceutical alternatives. Paroxetine mesylate generics are already registered in NL.

The excipients are: saccharine sodium, tween 80, ethanol, propylene glycol, acesulfame-K and mint flavour.

The product is packaged in a 20 ml amber glass bottle (Ph.Eur. Type III). In the neck of the bottle a vertical dropper device is firmly fitted. This type of glass bottle is commonly applied for the packaging of solutions. Because of the light susceptibility of the formulation, amber coloured glass is used to prevent as much as possible the colorization of the solution by light.The glass bottle is closed with a child resistant screw cap. The cap is supplied with a tamper evident ring. The child resistance screw cap is in compliance with "DIN EN ISO 8317".

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The purpose was to develop a pharmaceutical alternative for the tablet formulation. Therefore, in the bioequivalence studies, the product "Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution (Test product) was compared to Seroxat 20 mg, film-coated tablets (Reference product). One of the GMP batches was used as test product. The GMP batches were manufactured at a production scale conform the developed final procedure. The Reference product was obtained from the Dutch market. The batches are acceptable for the bio-equivalence study.

Excipients
All excipients comply with their Ph.Eur. monographs, except for mint flavour, for which the quality is in accordance with the European Directive EEC 88/388. The composition is laid down, including a GC-chromatogram and accompanied with technical data sheets.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. A flowchart of the manufacturing process is presented including in-process controls. Process validation data on the product has been presented for 3 production scaled batches in accordance with the relevant European guidelines.

Product specification
The finished product specification is adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, closure integrity, colour, clarity, dose and uniformity, deliverable volume, assay, related substances, and microbiological purity. Limits in the specification have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data have been provided for 3 batches from the proposed production site demonstrating compliance with the specification.

Overages
Requirement > 18.5 ml bottle fill. The bottle of the product contains 28 dosages of 20 drops. A total 28 dosages of 20 drops is equal to volume of 17.0 ml (i.e. 20 drops has a volume of 0.61 ml). From this it is concluded that an overfill of 1.5 ml (8%) is applied.

Stability tests on the finished product
Stability data on the product have been provided on 3 production scale batches stored at 25ºC/60%RH (12 months), 30ºC/65%RH (12 months) and 40ºC/75%RH (6 months) in accordance with applicable European guidelines. At accelerated and intermediate conditions after 6 months, no significant increase in impurities and decrease in assay are observed. In the 12 months samples of the ongoing stability study at accelerated condition, no ethyl methanesulfonate could be detected. At refrigerated condition after 6 months, no significant changes were observed. In the photo stability study no changes were observed in physical or chemical characteristics Based on the data submitted, a shelf-life could be granted of 24 months without specific storage conditions. The shelf-life has been changed into 3 years by a post-approval type IB variation (see variation NL/H/877/001/IB/011 in the '*steps taken after finalisation of the initial procedure*' table at page 12).
An in-use stability study showed that after opening the solution is stable for 28 days. The shelf-life of the finished product after first opening has been changed into 56 days by a post-approval type IB variation (see variation NL/H/877/001/IB/012 in the '*steps taken after finalisation of the initial procedure*' table at page 12).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present or used in the manufacture of this product, so a theoretical risk of transmitting TSE can be excluded.

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Paroxetine Kiron 33.1 mg/ml (= 20mg/20 drops) (Kiron Pharmaceutica B.V., the Netherlands), is compared with the pharmacokinetic profile of the Dutch reference product Seroxat 20 mg tablets (GSK, the Netherlands).

A randomised, two-period, cross-over, bioequivalence study was carried out under fasted conditions in 48 (including 4 alternates) healthy volunteers (26 males 22 female), aged 19-48 years. A dextromethorphan test was carried out to phenotype the CYP2D6. Subjects with a dextromethorphan/dextrorphan ratio less than 0.3 were classified as extensive metabolisers and were considered eligible for study participation. Subjects who have been already phenotyped as extensive metabolisers using the same procedure in the past with proper documentation were not tested again. Each subject received a single dose (20 mg; 1 tablet or 20 drops) of one of the 2 paroxetine formulations. The tablet was administered with 200 ml water under fasted conditions. For the test product, 20 drops were dissolved in 100 ml water and administered. Then the glass was rinsed with another 100 ml water, and administered too under fasted conditions. Standard meals were served 10.5 h before dosing, and at 4, 6, 9, 13, 15, 25, and 29 h post-dose. Subjects were free to drink additional supplied water or rose-hip tea from 4 hours post-dose. For each subject there were 2 dosing periods, with a washout period of 3 weeks. Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 32, 48, 60, and 72 hours after administration of the products.
Two subjects were withdrawn from the study before Period 2 due to an adverse event (bronchitis and tonsillitis) during the wash-out period. According to the protocol, 44 subjects (1-20, 22-33, 35-45 and 47) were eligible for pharmacokinetic analysis.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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

Treatment **N = 44**	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	97 ± 163	110 ± 218	4.6 ± 5.0	5.0 (0.5 – 8.0)	12 ± 6
Reference	87 ± 150	102 ± 221	4.2 ± 4.5	5.0 (1.0 – 8.0)	12 ± 6
***Ratio (90% CI)**	1.07 (0.98 - 1.15)	1.05 (0.97 - 1.14)	1.06 (0.97 - 1.16)	--	--
CV (%)	22.9	21.7	24.7	--	---

$AUC_{0-\infty}$ 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_{inf}, $AUC_{(0-t)}$ and C_{max} are in agreement with those calculated by the MAH and are within the acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of paroxetine under fasted conditions, it can be concluded that the reference tablet Seroxat (GlaxoSmithKline, The Netherlands) and test Paroxetine Kiron 20 mg/20 drops are bioequivalent with respect to the extent and rate of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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).

National application phase (before the MRP procedure)
After submission of the application in the Netherlands, several objections were raised by the MEB, which were resolved by the MAH before a marketing authorisation was granted in the Netherlands. The objections concerned the following issues:

- the high number of drops per dose and the difficulty of dosing (including a suggestion to use a dosing pipette instead of a dosing device)
- the risk of overdose (because of the relatively high concentration of the drops compared to the suspensions already registered)
- the accuracy of the dosing
- the claimed added value for facilitating gradual tapering off
- and the risk that the product will be used in children (because of its suitability for it)

During an oral explanation, the objections of the MEB were discussed with the MAH. Subsequently, the MAH answered the objections raised by the MEB in writing.

In their answer, the MAH argued that the number of drops corresponds to the mg dose needed, which makes it easy to determine the correct dose. Also, a switch to tablets and vice-versa should not be a problem. A dosing pipette was considered to be unsafe and unpractical as after unscrewing such a pipette there is risk of accidental spilling or swallowing of the whole solution at once. In addition such a device suffers from the risk of microbial contamination. Instead a dropping device was proposed which makes it more difficult to open the bottle and has the additional advantage of having an accurate drop size. With respect to the risk of overdose, additional warnings have been put on the bottle label and an additional description of use has been put on the box, leaflet and SPC. In the opinion of the MAH, the general warning in the SmPC/PIL with respect to use of SSRIs in children and adolescents prohibits use in children.
The accuracy of the dosing was shown in an in-use stablility study.
According to the MAH, the oral drop formulation facilitates gradual tapering off therapy by allowing individualised tapering off regimes. In addition, this formulation is considered useful for patients who have trouble swallowing tablets.

After evaluation of the MAH's answer, the MEB decided that a marketing authorisation could be granted provided that the MAH would commit to change the design of the dropping device in such a way that the opening of the bottle is more difficult. The use of the drops for gradual tapering off therapy is still questioned by the MEB for patients using the tablet formulation as it does not seem suitable to change the formulation during the tapering off formulation from tablets to oral drops.

Concerning the claimed indications, on 29 March 2005, the European Commission issued a Commission Decision on the Article 31 referral for paroxetine-containing products confirming the favourable benefit/risk profile for use in the treatment of major depressive episode, obsessive compulsive disorder, panic disorder with and without agoraphobia, social anxiety disorders/social phobia, generalised anxiety disorder and post-traumatic stress disorder.

MRP procedure/CMD(h)-referral
During the MRP procedure, a concern was raised regarding the practicality of counting up to 60 drops to achieve the required dose. Counting of more than 20 drops to obtain the required dose is not considered practical without undue increase in medication errors and possible overdose. There is therefore concern regarding the safety in use of the product.

At the CMD(h) meeting held in March 2007, the RMS presented its view and the MAH's written response were discussed. The MAH made use of an oral hearing. Following the discussion all involved Member States could agree on a proposal to adapt the SPC.

In section 4.2 of the SPC it is included that for doses requiring more than 40 drops, other pharmaceutical forms (e.g. tablets, oral suspension) should be considered. However if necessary, the patient should seek advice from the health care provider about alternative ways of administration, such as the use of an oral syringe. Moreover it will temporarily be included in the SPC that in case the health care provider advises the use of an oral syringe, the dropper device is removable, allowing the insertion of an oral syringe. The corresponding volumes required for doses greater than 40 drops are included as well in section 4.2 of the SPC. Inclusion of the possibility to remove the dropper device will only be temporary until the new presentation will be authorised.
The MAH has committed to submit a variation application to add another presentation, namely a bottle without dropper device, as soon as possible after finalisation of the procedure. A syringe will then be delivered separately. This commitment has been fulfilled by variation NL/H/0877/II/010, see annex II.

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 content of the SPC approved during the mutual recognition procedure is in accordance with the harmonised SPC for the innovator product Seroxat marketed by GlaxoSmithKline.

Readability test
The package leaflet 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 was diagnostic and scoring. This is acceptable because several questions were posed to identify potential problematic text items of the PIL in terms of traceability, comprehensibility and usability. Additionally the scoring percentages were met for all questions.
The test was conducted using an English patient information leaflet. The PIL readability testing was performed in three phases. Two participants were tested during the preliminary round of testing Thereafter, two test rounds were performed with 10 participants in each test round.
After the first test round, the PIL was amended. Most of the changes concerned an improvement of the lay-out. Furthermore, the headings in section “Possible side effects” were mentioned in more patient-friendly words. Also in the section “Taking other medicines”, more examples of medicines were given. Finally, in section “How to take Paroxetine Kiron 20 mg/20 ml drops” it was added that drinking alcohol should be avoided while taking Paroxetine Kiron 20 mg/20 drops.

Based upon the results, it can be concluded that the traceability, comprehensibility and usability of the information in the updated leaflet can be considered sufficient.

II OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution has a proven chemical-pharmaceutical quality and is a generic form 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 European guidance documents.

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

The content of the SPC approved during the MRP is in accordance with the harmonised SPC for the innovator product Seroxat. The SPC, PIL and packaging are in the QRD-template. Braille conditions are met by the MAH.

After submission of the national application (in the Netherlands before the MRP procedure), several objections were raised by the MEB, which were resolved by the MAH before a marketing authorisation was granted. Paroxetine Kion 33.1 mg/ml oral drops, solution was authorised in the Netherlands on 27 April 2006.

During the MRP procedure there was a referral to the CMD(h) on the grounds of a concern regarding the practicality of counting up to 60 drops to achieve the required dose. Counting of more than 20 drops to obtain the required dose was not considered practical without undue increase in medication errors and possible overdose. There was therefore concern regarding the safety in use of the product.

At the CMD(h) meeting held in March 2007 the RMS presented its view and the MAH's written response were discussed. The MAH made use of an oral hearing. Following the discussion all involved Member States could agree on a proposal to adapt the SPC.
In section 4.2 of the SmPC it is included that for doses requiring more than 40 drops, other pharmaceutical forms (e.g. tablets, oral suspension) should be considered. However if necessary, the patient should seek advice from the health care provider about alternative ways of administration, such as the use of an oral syringe. Moreover it will temporarily be included in the SmPC that in case the health care provider advises the use of an oral syringe, the dropper device is removable, allowing the insertion of an oral syringe. The corresponding volumes required for doses greater than 40 drops are included as well in section 4.2 of the SmPC. Inclusion of the possibility to remove the dropper device will only be temporary until the new presentation will be authorised.

The MAH has committed to submit a variation application to add another presentation, namely a bottle without dropper device, as soon as possible after finalisation of the procedure (see below). A syringe will then be delivered separately.

The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paroxetine Kiron 33.1 mg/ml oral drops, solution with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 29 March 2007.

PSUR
The MAH follows the schedule of the innovator, and participates in the EU Worksharing for PSUR assessment. At the closing of the procedure a 6 monthly PSUR cycle was agreed upon. At the time of writing the PSUR cycle is one year. The first PSUR covered the period from December 2006 to August 2007. The current PSUR will be submitted February 2010.

The common renewal date will be 29 March 2012.

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

- The MAH has committed to submit a variation application to add another presentation (in accordance with Cipralex), namely a bottle without dropper device, as soon as possible after finalisation of the procedure. A syringe will then be delivered separately. Also new SPC, PIL and labelling will be submitted to reflect these changes. The following should then be included in section 4.2 of the SPC (instead of the currently temporarily proposed text):
  "*The physician/specialist should consider the need for dosing in ml with a syringe instead of drops or prescribing another available pharmaceutical form for patients who might have potential problems with counting the required number of drops.*"
  Moreover the product name should be amended to include the strength in mg paroxetine/ml, as the current product name only provides a declaration of the strength in drops.
  This commitment has been fulfilled. See variation NL/H/877/001/II/010 in the "*Steps taken after finalisation of the initial procedure*" table.

Quality
- All studies will continue as described in the tables in the stability study information which can be found in Module 3.2.P.8.1 of the submitted reports.

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
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
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/877/001/IA/001	IA	17-7-2007	31-7-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Not including batch control/testing.	NL/H/877/001/IA/002	IA	17-7-2007	31-7-2007	Approval	N
Change in the name of the medicinal product in Austria.	NL/H/877/001/IB/003	IB	17-7-2007	16-8-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/877/001/IA/004	IA	17-7-2007	31-7-2007	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/877/001/IA/005	IA	17-7-2007	31-7-2007	Approval	N
Type II amendements of SPC and PIL for antidepressants.	NL/H/877/001/II/006	II	20-3-2008	4-4-2008	Approval	Y, Annex I
Change in the name of the medicinal product in Spain.	NL/H/877/001/IB/007	IB	23-4-2008	23-5-2008	Approval	N
Change in the name and/or address of a manufacturer of the active substance where no Ph. Eur. Certificate for Suitability is available.	NL/H/877/001/IA/008	IA	20-10-2008	3-11-2008	Approval	N
Change in the name and/or address of the MAH in Spain.	NL/H/877/001/IA/009	IA	5-11-2008	19-11-2008	Approval	N
Addition of a second presentation as result of a post-approval commitment during the MRP.	NL/H/877/001/II/010	II / post-approval commitment	10-2-2009	27-8-2009	Approval	Y, Annex II
Change in the shelf-life of the finished product as packaged for sale. Extension of the shelf-life from 24 to 36 months.	NL/H/877/001/IB/011	IB	3-8-2009	2-9-2009	Approval	N
Change in the shelf-life of the finished product after first opening. Extension of the shelf life of the finished product after first opening the solution from 28 to 56 days.	NL/H/877/001/IB/012	IB	3-8-2009	2-9-2009	Approval	N

Annex I – Type II variation, amendments of SPC and PIL for antidepressants NL/H/0877/II/006

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.

Annex II, post-approval commitment, variation NL/H/0877/II/010

I. Recommendation

Based on the review of the data on quality, the RMS considers that the variation application NL/H/0877/II/010 for Paroxetine Kiron 33.1 mg/ml, drops for oral use, solution, (Paroxetine mesylate), in the treatment of Major Depressive Episode, Obsessive Compulsive Disorder (OCD), Panic Disorder with and without agoraphobia, Social Anxiety Disorder/Social phobia, Generalised Anxiety Disorder and Post-traumatic Stress Disorder, for the following proposed changes,

"*addition of another presentation, bottle with LDPE dropper, HDPE child-resistant closure* ***and a syringe (polypropylene/polyethylene)****, change of the product name as committed during the MRP in 2007 and consequential changes to SPC/labelling and PIL and some sections of CTD (3.2.P.1 and 3.2.P.7)*",

is approvable.

II. Executive Summary

II.1 Scope of the variation

At the finalisation of the MRP NL/H/877/01/MR in March 2007, the MAH committed to submit a variation application to add another presentation (with a syringe) for the product and to amend the product name to include the strength in mg paroxetine/ml.

An optional syringe for oral administration of more than 40 drops has been added to the packaging. This syringe is added due to comments of a CMS, that more than 20 drops are not easy to count and is subject to errors.
As a result the SPC, PIL and labelling as well as some sections of the CTD (3.2.P.1, 3.2.P.2 and 3.2.P.7) have been adapted.

III Scientific discussion

III.1 Quality aspects

The MAH has added to the packaging an optional syringe for oral administration of more than 40 drops. This syringe is added due to comments of a CMS, that more than 20 drops are not easy to count and is subject to errors.

During the CMD(h) meeting in March 2007 it was agreed that counting of more than 40 drops to obtain the required dose is not considered practical without undue increase in medication errors and possible under- or overdose. Therefore there was concern regarding the safe use of the product. The syringe is added to allow safe dosing of a larger number of drops. The syringe is used to withdraw an amount in millilitres of the product. The syringe can be used in the range of 0.6 till 1.8 ml, corresponding to 20 till 60 drops. Therefore, the syringe is considered a safer alternative to counting drops.

The modules 3.2.P.1, 3.2.P.2 and 3.2.P.7 have been updated.

The MAH updated Module 3.2.P.1 on the description of the drug product to include "an oral syringe may be enclosed". In addition, an overview of ingredients was provided.

The MAH updated Module 3.2.P.2 on the development of the packaging and dropper system with a description of the development of the oral syringe. Drop weights before and after the use of the syringe as well as the weight of specified volumes taken from the vials with different syringes were determined.

In addition an R&D report was presented that demonstrated compliance with the requirements of the Ph.Eur. 2.9.27 for the doses 1.2 ml and 1.8 ml. Furthermore, the appearance of the syringe tip was monitored after cleaning. No visual particles or crystallization is observed after 3 days of storage.

III.2. Product information

A specification for the syringe (with sufficient detail of the syringe (drawing, materials, dimensions etc.) was included in module 3.2.P.7.

The RMS advised to set a maximum to the number of drops from a safety point of view where the syringe could compensate for the higher dosing. The MAH agreed and implemented the following changes in the SPC:

- A maximum number of drops has been defined. Therefore dosages from 10 to 30 mg (10 to 30 drops) should be administered using the dropper applicator (counting more than 40 drops to obtain the required dose could lead to dosing errors).
- As a consequence, the syringe should be used to administer doses from 40 mg to 60 mg (1.2 to 1.8 ml).
- The table and the wording of section 4.2 have been modified accordingly. The dosage and the device to use for administration have been set as follows: |
  10-30 mg: dosing in drops/application dropper
  40-60 mg: dosing in ml/syringe
- A picture and description illustrating the use of the oral syringe have been added.
- The paragraph on the use of the dropper applicator vs. the oral syringe has been split out in two sections to more clearly explain the different ways of administration.

The revisions are agreed by the RMS.

The MAH submitted a revised PIL, based on the comments in the PVAR. The proposed changes for the dosing section are agreed upon.

User test
No user test has been submitted. The MAH requested that the user test be undertaken post variation. after agreement has been reached between RMS and CMS of the PIL text.

The RMS agrees to the proposal to submit post-approval results of a user test. However, this should be submitted within 3 months after closure of the variation procedure. As the change in the product information is considered major, the product cannot be marketed until the results of the user test have been assessed and agreed upon.

A revised version of the labelling is provided. The changes are agreed upon.

IV Overall conclusion

As committed during the MRP procedure the MAH has submitted a type II variation to add a second presentation with a syringe to facilitate dosing of more than 40 drops. Moreover the product name has been changed to include the strength in mg/ml as requested.
Amended versions of SPC/PIL and labelling have been submitted and the modules 3.2.P.1, 3.2.P.2 and 3.2.P.7 have been updated.
The proposed variation is approvable. A user test should be undertaken, the results of which should be submitted within 3 months. The product cannot be marketed until the results of the user test have been assessed and agreed upon.