

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Clozapine CF 25 mg, 100 mg and 200 mg, tablets  
Centrafarm B.V., the Netherlands**

**clozapine**

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.

It reflects the scientific conclusion reached by the MEB 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.

**Registration number in the Netherlands: RVG 106835-106837**

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Pharmacotherapeutic group:	antipsychotics, diazepines, oxazepines, thiazepines and oxepines
ATC code:	N05AH02
Route of administration:	oral
Therapeutic indication:	in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents; psychosis during the course of Parkinson's disease when standard treatment has failed.
Prescription status:	prescription only
Date of authorisation in NL:	9 April 2013
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

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

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Clozapine CF 25 mg, 100 mg and 200 mg, tablets from Centrafarm B.V. This decision was reached after an appeal procedure initiated by the applicant. This procedure is discussed in section II.3 'Clinical aspects, on pages 7-8 of this report.

The date of authorisation was on 9 April 2013 in the Netherlands. The indications are described below:

### Schizophrenia

The product is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

### Psychosis in the course of Parkinson's disease

Clozapine CF 25 mg and 100 mg are also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

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

Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics. In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub> and D<sub>5</sub> receptors, but shows high potency for the D<sub>4</sub> receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.

This national procedure concerns a generic application claiming essential similarity with the innovator product Leponex tablets, which has been registered in the Netherlands by Novartis Pharma B.V. since 1988. The product is available in 25 mg and 100 mg tablet strengths (NL License RVG 10459-10460), which are part of MRP UK/H/0583/001-002.

The marketing authorisation for the 25 mg and 100 mg strengths was granted based on article 10(1) of Directive 2001/83/EC. Clozapine CF 200 mg was authorised based on article 10(3), a hybrid application with a difference in strength. Moreover, the indication for the 200 mg does not include psychosis in Parkinson's disease.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Clozaril® 25 mg tablets (Novartis UK; administered as half a tablet, i.e. 12.5 mg). 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. This 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, which is acceptable for a generic application.

## 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 clozapine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a yellow crystalline powder, which is freely soluble in methylene chloride and soluble in ethanol. It dissolves in dilute acetic acid.

The Active Substance Master File (ASMF) procedure is used for one manufacturer of 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/EMA 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.

For the second manufacturer, the CEP procedure is used. 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

For the CEP holder no details on the manufacturing process have been included, which is acceptable. For the ASMF holder, the described synthesis comprises one synthetic step and purification. The manufacturing process has been adequately described. The starting materials of the synthesis are considered acceptable. No class 1 solvents are used. Clozapine has been adequately characterised.

#### Quality control of drug substance

The drug substance specification of the MAH is in line with the Ph.Eur., with additional requirements for particle size distribution and residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for two production-scale batches of the first supplier, and for three production-scale batches of the second manufacturer.

#### Stability of drug substance

The active substance from the first supplier is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Stability data on the active substance from the second manufacturer have been provided for five full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (12 months). No changes were observed

during storage. Based on the stability data provided the proposed re-test of 3 years without special storage conditions was granted.

## **Medicinal Product**

### Composition

Clozapine CF 25 mg and 100 mg are round, yellow, flat bevel-edged tablets with '25' or '100' and a breakline on one side and plain on the other side.

Clozapine CF 200 mg is an oval shaped, yellow tablet with '200' on one side and a breakline on the other side.

All three tablets can be divided into equal halves.

The tablets are packed in PVC/PVDC-Alu blisters and a HPDE bottles with PP, child-resistant and tamper-evident cap.

The excipients are: lactose monohydrate, microcrystalline cellulose, povidone K30, sodium starch glycolate and magnesium stearate.

The three strengths are fully dose proportional.

### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies and comparative dissolution studies. Dissolution profiles were demonstrated to be similar for each of the different tablet strengths.

A bioequivalence study was performed with half a tablet of the 25 mg strength. The batch used in the bioequivalence studies has the same composition and is manufactured in the same way as the future commercial batches. The composition of the Dutch and UK reference products is identical. Hence, a bioequivalence study performed with the UK reference product is acceptable.

All tablet strengths bear a breakline for which compliance with the Ph.Eur. criteria was demonstrated. The pharmaceutical development of the product has been adequately performed.

### Manufacturing process

The manufacturing process is divided into the following steps: blending, wet granulation, blending, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for three full-scale batches of each strength.

### Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

### Quality control of drug product

The product specification includes tests for description, identification, hardness, dimensions, friability, average weight, loss on drying, related substances, assay, uniformity of content of tablet halves, uniformity of dosage units, dissolution and microbial limits. The release and end of shelf-life limits are identical, except for hardness. This is acceptable since increases in hardness were observed during stability studies. The drug product specification is considered acceptable.

The analytical methods have been adequately described and validated, and are stability indicating. Batch analytical data from the proposed production site have been provided on three full-scale batches of 100 mg and 200 mg tablets and on four pilot-scale batches of 25 mg tablets, demonstrating compliance with the release specification.

#### Stability of drug product

Stability data on the product has been provided on the following batches stored at 25°C/60% RH (24-60 months) and at 40°C/75% RH (6 months):

- 25 mg tablets in blister; 3 full-scale batches (24 – 36 months)
- 100 mg tablets in blister; 4 full-scale batches (24 – 60 months)
- 200 mg tablets in blister; 3 full-scale 2 pilot-scale batches (24 – 48 months)
- 25 mg tablets in bottle; 5 full-scale batches (24 – 48 months)
- 100 mg tablets in bottle; 3 full-scale and 1 pilot-scale batches (24 – 48 months)
- 200 mg tablets in bottle; 5 full-scale and 2 pilot-scale batches (24 – 48 months)

The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packages.

Increases in hardness and total impurities were observed at accelerated conditions in all strengths, however, all results remained well within the specification limits. The increase in hardness was more pronounced in the 100 mg tablets and in the blister. At long term conditions an increase in hardness was also observed in the 100 mg tablets in blister and bottle and in the 200 mg tablet in blisters, although less pronounced than at accelerated conditions.

All other parameters examined remained relatively stable throughout the test periods for all strengths and at both test conditions. Photostability study was performed in accordance with Nfg. No changes were observed in appearance, assay, related substances or dissolution. The drug product is considered photostable.

Based on the stability data provided the proposed shelf life of 4 years without special storage conditions can be granted.

Stability data has been provided demonstrating that the product remains stable for 3 months following first opening of the container when stored without special storage conditions.

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

Lactose monohydrate is the only excipient of animal origin. The milk used for the manufacture is sourced from healthy animals under the same conditions as milk collected for general human consumption (in compliance with EMEA/410/01 and EMEA/CPMP/571/02).

## **II.2 Non-clinical aspects**

This product is a generic formulation of Leponex, which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

#### **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 clozapine 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**

Clozapine 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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Clozapine CF 25 mg (Centrafarm B.V., the Netherlands) is compared with the

pharmacokinetic profile of the reference product Clozaril® 25 mg tablets (Novartis Pharmaceuticals UK Ltd). The administered dose was 12.5 mg (half a tablet).

*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 the Dutch and UK reference products. The UK product is representative of the Dutch product Leponex tablets.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, with mean age of 26.9 years. Each subject received a single dose (12.5 mg; ½ x 25 mg) of one of the 2 clozapine formulations. The two halves obtained after dividing the 25 mg tablet were weighed and evaluated as acceptable when their single weight fell within the range 50% ± 5% of the original weight. The tablet was orally administered after an overnight fast. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours post-dose after administration of the products.

The study design is appropriate, as it is in accordance to the Guideline on the Investigation of Bioequivalence. Based on the known half-life of clozapine (8-10 hours) the wash-out period of 5 days is sufficient. Usually, a bioequivalence study for a product range is conducted with the highest dosage form, but due to safety aspects the dosage of 12.5 mg was chosen for the bioequivalence study. This is acceptable.

*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*

Twenty-five healthy Caucasian male volunteers were enrolled. Twenty-four were included and all completed the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> (median, range)) of clozapine under fasted conditions.

Treatment N=24	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	248 ± 90	262 ± 94	26 ± 9	1.5 (1-5)	17 ± 5
<b>Reference</b>	268 ± 113	281 ± 119	29 ± 10	1.5 (1-5)	16 ± 4
<b>*90% CI</b>	0.88-1.04	0.89-1.04	0.83-0.95	--	--
<b>CV (%)</b>	--	--	--	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of clozapine under fasted conditions, it can be concluded that Clozapine CF 25 mg and Clozaril 25 mg tablets are bioequivalent with respect to rate and extent 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).

Clozapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of clozapine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

#### *Biowaiver*

The MAH applied for a biowaiver for the 100 mg and 200 mg strengths, as the following conditions are fulfilled:

- the different strengths are manufactured by the same manufacturer and production process.
- pharmacokinetics have been shown to be linear over the therapeutic dose range;
- the qualitative composition of the different strengths is the same;
- the ratio between the active substance and the excipients is the same.

However, the Board noted the requirement that dissolution profiles should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study. Insufficient data were provided to demonstrate comparable dissolution profiles among the different strengths.

#### **Initial refusal decision**

The following deficiencies were noted, which precluded a recommendation for marketing authorization:

- As the biobatch had expired, the dissolution tests were performed with another batch. The MEB was concerned that the batch used in dissolution testing was not representative of the biobatch. It was not clear whether the manufacturing process was identical and if the batch size was commercial scale.
- Moreover, it was not acceptable that a different bioanalytical laboratory performed the testing for the long term stability period of 159 days as the conditions (e.g. storage, handling and processing, instrumentation, etc.) were not comparable to the initial site.
- In accordance with the guidelines complete comparable dissolution data should be provided for the 100 and the 200 mg tablets at pH values of 4.5 and 6.8 for extrapolation of the results obtained in the bioequivalence study. Because of the solubility limitations of clozapine at high pH, dissolution testing at pH 6.8 should be performed at the same dose (*i.e.* 1 x 200 mg, 2 x 100 mg, 8 x 25 mg and 8 x 12.5 mg) and factor  $f_2$  should be computed. For pH 4.5, similarity for the 100 mg was not shown as the dissolution did not approach 85% in 15 minutes, but in 30 minutes. The Board considered that, in order to prove similarity, dissolution testing should be performed at time points 5, 10, 15 and 30 minutes and the  $f_2$  values should be calculated.

In view of these remaining issues, the MEB considered that a marketing authorisation could not be granted. The Board informed Centrafarm B.V. of its refusal decision on 10 April 2012.

#### **Appeal procedure**

Centrafarm B.V. submitted an appeal on 16 May 2012 against the MEB's decision to refuse granting a marketing authorization for Clozapine CF, making reference to the Dutch General Administrative Law Act. On 17 December 2012, the MEB appeals committee held a hearing with the objecting party as part of this appeal procedure. The objecting party presented its views and substantiated its objections to the MEB's decision. These concerned both legal and contextual aspects.

The MEB declared that the objections concerning legal aspects are unfounded. The appropriate procedures were followed.

With respect to contextual aspects, Centrafarm submitted additional data, as required during the national application procedure. Based on the assessment of these results, the Board came to the following conclusions:

- It was adequately demonstrated the similarity of the batch used in dissolution testing with the biobatch. The use of this batch in the comparative dissolution studies is therefore considered acceptable.
- With regard to the analytical center which performed the bioanalytical testing, Centrafarm argues that this site is not operational anymore. Another analytical center performed the required long-term stability testing using the original analytical method used by the initial site. Some amendments were done due to the different instrumentation. The requirements for method validation were met in the re-validated method. The changes made are considered acceptable since these are adjustments necessary to fit in to the different instrumentation.
- The requested additional dissolution data for each strength, 25 mg, 100 mg and 200 mg, performed at the same dose (200 mg) were submitted. At pH 4.5, the dissolution profiles are considered similar as more than 85% dissolved in 15 min from all tablet strengths. At pH 6.8, the dissolution is very limited (*i.e.* max 15%). However, it was sufficiently demonstrated that dissolution is also similar for all tablet strengths at this pH value.

Based on these conclusions, the MEB considers that the results obtained in the bioequivalence study can be extrapolated to the other tablet strengths. The benefit/risk profile of Clozapine CF 25 mg, 100 mg and 200 mg tablets is positive. Therefore the MEB considered that the contested decision of 10 April 2012 should be revised. The Board decided to grant a marketing authorisation for Clozapine CF. The decision on appeal was announced to Centrafarm B.V. on 18 April 2013.

#### Risk management plan

Clozapine was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clozapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. 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. A detailed European Risk Management Plan was not necessary for this product at the time of application.

#### **Product information**

##### SmPC

The SmPC, package leaflet and labelling are in the agreed templates. The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Leponex tablets (UK/H/0583/001-002). The different indication for Clozapine CF 200 mg, which is not indicated for psychotic disorders occurring during the course of Parkinson's disease, is acceptable, as this indication was also not granted for another clozapine 200 mg generic.

##### Readability test

The package leaflet (PL) is highly in accordance with the leaflet for Leponex. The PL has not been evaluated via a user consultation study.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clozapine CF 25 mg and 100 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Leponex 25 mg and 100 mg tablets. Clozapine CF 200 mg is an approvable hybrid form. Leponex is a well-known medicinal product with an established favourable efficacy and safety profile.

Initially, in the meeting of 23 February 2012, the Board discussed the application and concluded that the bioequivalence results with the 25 mg strength could not be extrapolated to the higher strengths. This negative outcome was implemented by the Board in a national refusal decision on 10 April 2012. The MAH appealed against this refusal decision, making reference to the Dutch General Administrative Law. During the appeal procedure sufficient additional data were provided to substantiate a biowaiver for the 100 mg and 200 mg tablets. Therefore the Board reached its final, positive decision in the meeting of 4 April 2013.

In conclusion, the MEB considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Clozapine CF 25 mg, 100 mg and 200 mg tablets were authorised in the Netherlands on 9 April 2013.

There were no post-approval commitments made during the procedure.

## 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
SmPC	Summary of Product Characteristics
$t_{1/2}$	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	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 manufacturer responsible for importation and/or batch release. Replacement or addition of primary and secondary packaging sites;	IA/G	4-9-2013	3-10-2013	Approval	N
Change in the specification parameters and/or limits of the finished product: addition or replacement of a specification parameter with its corresponding test method as a result of a safety or quality issue.	IB	5-3-2014	24-3-2014	Approval	N
Introduction of the Summary of Pharmacovigilance System Master File.	IA	20-5-2015	19-6-2015	Approval	N
Update of the SmPC and PL in accordance with the reference product Leponex.	IB	1-3-2016	28-4-2016	Approval	N
Submission of an updated Certificate of Suitability for an active substance manufacturer.	IA	15-3-2016	12-4-2016	Approval	N
Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place.	IA	6-11-2017	6-12-2017	Approval	N
Adaption of SmPC and PL with the text from reference product Leponex tablets.	IB	20-11-2017	20-12-2017	Approval	N
Labelling changes.	PIL Art. 61	6-2-2018	12-3-2018	Approval	N