COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pregabaline CNX 82.5 mg, 165 mg and 330 mg prolonged-release tablets (pregabalin)

NL/H/5677/001-003/DC

Date: 3 September 2024

This module reflects the scientific discussion for the approval of Pregabaline CNX 82.5 mg, 165 mg and 330 mg prolonged-release tablets. The procedure was finalised on 21 December 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pregabaline CNX 82.5 mg, 165 mg and 330 mg prolonged-release tablets, from CNX Therapeutics Ireland Limited.

The product is indicated for the treatment of peripheral and central neuropathic pain in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application since pregabalin was solely registered as pharmaceutical forms of hard capsules and solution in the Netherlands and Europe. Both are immediate release formulations. With this application, the MAH intended to register prolonged release tablets.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules, which has been registered in the EU via a centralised procedure (EU/1/04/279) since 6 July 2004.

The concerned member states (CMS) involved in this procedure were Cyprus and Malta.

Scientific advice

The MAH requested scientific advice twice at the Dutch Medicines Evaluation Board. These advices focused on the design of the studies to demonstrate equivalence with the reference product Lyrica hard capsules. With the first advice, the MAH provided information that in the United States, Lyrica modified release tablets are registered and bioequivalence data with this product was provided as well. However, since the Lyrica modified release tablets are not registered in Europe, this data could not be used. The MAH proposed different designs and waivers concerning clinical and non-clinical data. During the second advice, data from the first round of studies was discussed, and a pharmacodynamics /efficacy non inferiority study was proposed as the bioequivalence for C_{min} could not be demonstrated.

Indication

The originally proposed indication was: “treatment of neuropathic pain, epilepsy and generalised anxiety disorder”. During the application the MAH changed the indication to: “treatment of peripheral and central neuropathic pain in adults”.

II. QUALITY ASPECTS

II.1 Introduction

Pregabaline CNX is an oval, unscored prolonged-release tablet. Each prolonged-release tablet contains as active substance 82.5 mg, 165 mg or 330 mg of pregabalin.

- Pregabaline CNX 82.5 mg is a white prolonged-release tablet, blank on one side and imprinted “ALV 379” in black ink on the other side.
- Pregabaline CNX 165 mg is a yellow prolonged-release tablet, blank on one side and imprinted “ALV 380” in black ink on the other side.
- Pregabaline CNX 330 mg is a pink prolonged-release tablet, blank on one side and imprinted “ALV 381” in black ink on the other side.

The excipients are:
Tablet core - hypromellose, hydroxypropyl cellulose (E463), basic butylated methacrylate copolymer (E1205), crospovidone (Type A), magnesium stearate (E470b) and colloidal anhydrous silica (E551).

Tablet coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521) and talc (E553b).

The tablet coating of Pregabaline CNX 165 mg furthermore contains yellow iron oxide (E172) and red iron oxide (E172).

The tablet coating of Pregabaline CNX 330 mg furthermore contains red iron oxide (E172) and black iron oxide (E172).

Printing ink - shellac glaze, black iron oxide (E172) and propylene glycol (E1520).

The tablets are packed in carton box containing white, wide-mouthed, round high-density polyethylene (HDPE) container with child-resistant white cap with liner and one desiccant bag.

II.2 Drug Substance

The active substance is pregabalin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder with only one polymorphic crystalline form and is sparingly soluble in water. The active substance exhibits isomerism and contains one chiral centre.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible

Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests on impurities for the related substances and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for two batches of each supplier.

Stability of drug substance
The active substance from site I is stable for 60 months 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 site II have been provided for 30 batches stored at long term conditions (25°C/60% RH, 60 months), and six batches stored at accelerated conditions (40°C/75% RH). In accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The working principles of the prolonged release, and the choice for wet granulation as manufacturing process have been adequately explained. Comparative dissolution data has been submitted for the 165 mg strength in relation to the 82.5 mg and the 330 mg strength. An in-house dissolution method has been developed with acceptable limits, and discriminatory power has been adequately demonstrated. The pharmaceutical development has been adequately performed.

Manufacturing process
The product is manufactured by wet granulation through the following steps: screening, granulation, drying, milling, final blending, lubrication, compression, film coating, printing, and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for seven batches (two batches of the 82.5 mg strength, four of the 165 mg strength and one batch of the 330 mg strength) from manufacturing site I and three batches of each strength from site II, in accordance with the relevant European guidelines.

Control of excipients

The excipients in the core tablets comply with Ph.Eur. and in-house requirements, as well as relevant EC directives. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, uniformity of dosage units, assay, related substances, dissolution, residual solvents and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 6 batches of the 82.5 mg strength, 8 batches of 165 mg and 6 batches of the 330 mg strength from production site I have been provided, demonstrating compliance with the specification. Batch analytical data from three batches of each strength from production site II have been provided, demonstrating compliance with the specification.

Stability of drug product

Site I

Stability data on the product have been provided for at least five batches of each strength in the proposed packaging stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in HDPE containers. For the 82.5 mg strength, stability data was also collected under intermediate conditions at 30°C/65% RH (12 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. Photostability studies have been conducted conform to ICH Q1B from which it can be concluded that pregabalin is photostable in the current formulation. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions for the 82.5 mg strength are 'Do not store above 30°C'. No special storage precautions are required for the 165 mg strength and 330 mg strength.

Site II

Three batches of each strength have been put on stability in the HDPE container, but only the initial measurement has been performed.

The HDPE container, cap, and desiccant used for the batches manufactured at site II conforms to the same specification as the HDPE container used for the batches at site I.

Based on this information, comparable batch analytical results, and the fact that both sites share the same manufacturing process, which has been adequately validated at site II, the stability data collected in the HDPE container at site I can be regarded as representative for the product manufactured (and packed in HDPE containers) at site II.

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

The MAH has indicated no ingredients of human origin are present, and only Shellac is present of animal (insect origin), which is not impacted in TSE/BSE. A TSE/BSE statement has been provided by the MAH regarding the product, which is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pregabaline CNX is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Pregabalin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. Additionally, the MAH has performed two bioavailability studies and a PD/efficacy non-inferiority trial.

IV.2 Pharmacokinetics

The MAH conducted a bioavailability study in which the pharmacokinetic profile of the test product Pregabaline CNX 330 mg prolonged-release tablets (CNX Therapeutics Ireland Limited, Ireland) was compared with the pharmacokinetic profile of the reference product Lyrica 150 mg hard capsules (Pfizer Manufacturing Deutschland GmbH, Germany). In the second bioavailability study, the subjects received 82.5 mg and 330 mg of the test product in different sequences.

The choice of the reference product in the bioavailability study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioavailability batch was identical to the formula proposed for marketing.

Biowaiver

The MAH was granted a biowaiver for *in vitro* bioequivalence studies for the 165 mg strength, based on these criteria:

a. the 82.5 mg, 165 mg and 330 mg strength are manufactured by the same manufacturing process,
b. the qualitative composition of the three strengths is the same,
c. the composition of the strengths are quantitatively proportional,
d. appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution of the 82.5 mg, 165 mg and 330 mg test products were investigated according to the EMA Bioequivalence guideline at pH 1.2 (0.1 N HCl), pH 4.5 (sodium acetate buffer) and pH 6.8 (potassium phosphate buffer). The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioavailability studies

Study I (single dose and multiple dose)

Design

A single-dose and multiple-dose, randomised, open-label, two-period, two-sequence, two-treatment, single-centre, crossover, comparative bioavailability study was carried out under fasting (single dose) and fed (multiple dose) conditions in 16 healthy male subjects, aged 26-60 years. In each study period, subjects were dosed according to the randomisation scheme with one of the two pregabalin formulations (330 mg of test product or 150 mg of reference product). There were two dosing periods, separated by a washout period of at least 7 days.

First dosing of test product and reference product: the tablet was orally administered with 240 mL water after at least an 8-hour fasting period.

Second dosing of reference product: the tablet was orally administered with 240 mL water after at least an 6-hour fasting period.

Dosing on day 4 evening (test product): following at least an 8-hour fasting period, subjects were started an high-fat, high-calorie meal 30 minutes prior to dosing. The tablet was orally administered with 240 mL water, 30 minutes after the start of the high fat/high calorie meal.

Dosing on day 5 morning (reference product): following at least an 6-hour fasting period, subjects were started an high-fat, high-calorie meal 30 minutes prior to dosing. The tablet was orally administered with 240 mL water, 30 minutes after the start of the high fat/high calorie meal.

Blood samples were collected at the following time points in each study period:
For Test Product A:

- Day 1: Prior to the evening dose at pre-dose (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 23.75 post dose.
- Day 3: Pre-dose (0 hour), prior to the evening dosing.
- Day 4: Prior to the evening dose at pre-dose (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20 and 24 hours post dose.

For Reference Product B:

- Day 1: Prior to the evening dose at pre-dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 5, 8, 11.75, 12.25, 12.5, 12.75, 13, 13.25, 13.5, 14, 16, 18, 20, and 23.75 hours post first dose.
- Day 4: Prior to the morning dose (12 hours post-dose of day 3 evening dose) and prior to the evening dose at pre-dose (0 hour) and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 2, 3, 5, 8, 11.75, 12.25, 12.5, 12.75, 13, 13.25, 13.5, 14, 16, 18, 20 and 24 hours post evening dose.

The design of the study 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
All 16 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin, 330 mg (test) / 150 mg (reference) under fasted conditions.

Treatment N=16	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	26631 ± 13093	29791 ± 15035	2369 ± 663	4 (1 - 10)
Reference	54870 ± 6863	64948 ± 8999	6060 ± 1512	1.0 (0.5 - 1.5)
***Ratio (90% CI)**	0.45 (0.39 - 0.52)	0.42 (0.37 - 0.49)	0.39 (0.33 - 0.46)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin, 330 mg (test) / 150 mg (reference) under fed conditions.

Treatment N=16	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	60293 ± 10483	-	3907 ± 718	12 (5 – 14)
Reference	58805 ± 8670	-	4113 ± 641	3.00 (1.25 – 4.00)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	-	0.95 (0.88 – 1.02)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study II (dose proportionality and food effect study)

Design

An open-label, randomised, three-period, two-treatment, six-sequence, crossover, balanced, single dose food effect and dose proportionality study was carried out under fasted and fed conditions in 36 healthy male subjects, aged 18-43 years.

After fasting of at least 6 hours, a single (1 × 330 mg) oral dose of the test product was administered to the subject in the evening (fasting condition) and a single (1 × 82.5 mg) or (1 × 330 mg (T2) oral dose of investigational product was administered to the subjects in the evening (fed condition) at 30 minutes after serving the standardised high-calorie & high-fat dinner. The tablets were orally administered with 240 mL water.

The subjects received the test product (82.5 mg or 330 mg pregabalin) in the study as per the randomisation schedule. The following sequences were possible:

- 330 mg (fasting) – 330 mg (fed) – 82.5 mg (fed)
- 82.5 mg (fed) – 330 mg (fasting) – 330 mg (fed)
- 330 mg (fed) – 82.5 mg (fed) – 330 mg (fasting)
- 82.5 mg (fed) – 330 mg (fed) – 330 mg (fasting)
- 330 mg (fed) – 330 mg (fasting) – 82.5 mg (fed)
- 330 mg (fasting) – 82.5 mg (fed) – 330 mg (fed)

There were 3 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 30, 36 and 48 hours after administration of the products.

The design of the study 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

A total of 36 subjects were dosed in period I of the study. Four subjects dropped out. Two subjects dropped out because of a positive drug/alcohol test. Another subject dropped out because of vomiting after 11 hours post-dose in period III. The last subject dropped out because he did not report for subsequent periods of study after period I. Finally, 32 subjects were eligible for pharmacokinetic analysis.

Table 3. Dose proportionality: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin, 82.5 mg (dose-normalised to 330 mg) and 330 mg under fed conditions.

Treatment N=32	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
82.5 mg (fed)	59.1 ± 13.9	59.8 ± 13.9	3.83 ± 1.00	9 (2 – 16)
330 mg (fed)	55.6 ± 12.3	56.1 ± 12.6	3.59 ± 0.70	8 (4 – 12)
***Ratio (90% CI)**	1.06 (1.02 – 1.11)	-	1.05 (1.00 – 1.11)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 4. Food effect: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin, 330 mg under fasted and fed conditions.

Treatment N=32	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
330 mg (fed)	55.6 ± 12.3	56.1 ± 12.6	3.59 ± 0.70	8.00 (4.00 – 12.00)
330 mg (fasted)	28.2 ± 8.04	28.4 ± 8.07	2.42 ± 0.54	4.00 (1.50 – 6.00)
***Ratio (90% CI)**	2.01 (1.85 – 2.17)	-	1.49 (1.40 – 1.59)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioavailability studies

The results of the multiple dose fed study showed that $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of the test product were comparable to those of the reference product. However, the the ratio of the pharmacokinetic parameters between the test group and the control group for $C_{min,ss}$ was below 80%.

The results of the dose proportionality study showed that the pharmacokinetics of pregabalin are linear for the test product, over the dose range 82.5-330 mg. Considering that for the reference product (immediate release) linear pharmacokinetics was proven in the range 75-600 mg, linear pharmacokinetics is also expected for the test product up to 660 mg by using multiples of the single units.

The results of the food effect study showed that the test product is subject to a food effect, given the fact the 90% confidence interval calculated for AUC_{0-t} and C_{max} was not within the range 80.00% - 125.00%, and t_{max} was not similar, when comparing a single dose of 330 mg under fed conditions with a single dose of 330 mg under fasting conditions.

The MEB has been assured that the bioavailability 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).

IV.3 Pharmacodynamics, clinical efficacy and safety

Bioequivalence with the reference product was not fully demonstrated by bioavailability studies. To demonstrate clinical irrelevance of the observed difference in exposure with the reference product, a pharmacodynamic/efficacy non-inferiority trial was conducted to evaluate the non-inferiority of Pregablin prolonged release tablets compared to the reference immediate release product (Lyrica), its efficacy compared to placebo, and the general safety and tolerability of the product.

Design

A randomised, double-blind, double-dummy, multiple-dose, multicentre, three-arm, parallel study was carried out in 453 male and female subjects with diabetic peripheral neuropathy, aged 41-64 years. Each subject received one of the two pregabalin formulations or a placebo.

Treatment for test arm was started at a dose of 165 mg per day, once daily, orally and treatment for reference arm was started at a dose of 150 mg per day, orally, in two or three divided doses. Based on the subject response, and tolerability, the dose for subjects with test arm was adjusted up or down by 82.5 mg/day or 165 mg/day, at each titration visit; and for subjects with reference arm, the dose was increased gradually to 300 mg per day in two or three divided doses, after an interval of 7 days. The optimal dose of study medication was determined in the first 4 weeks after randomisation. The medication dose was titrated at weekly intervals, based on efficacy and tolerability, up to a maximum dose of 660 mg (for test product) or 600 mg (for reference product). The optimised dose was used, in a fixed manner, during the next 9 weeks of this study. The total duration of the study for each subject was approximately 17 weeks.

Statistical methods
The methods used in this study for the pharmacodynamic calculations and statistical evaluation are considered acceptable.

Results
A total of 453 subjects met eligibility criteria and were randomised in the study. Reasons for discontinuation from the study (N=44) were withdrawal by subjects (N=33), lost to follow-up (N=6), non-compliance to study requirements (N=1), physician decision (N=2), and other (N=2). Finally, 409 subjects were eligible for pharmacodynamic analysis.

Efficacy
Mean ± SD of change in mean weekly pain score from baseline to end of treatment for test, reference and placebo group were -3.445 ± 1.4855, -3.604 ± 1.3711 -3.166 ± 1.7685, respectively. Reduction observed in mean weekly pain score was comparable between test and reference treated group and lower in placebo treated group.

Safety
No serious adverse even was reported during the study. A total of 147 adverse events (AEs) were reported in 101 subjects during the study. All the AEs were reported after randomisation and referred as treatment-emergent adverse events (TEAEs).
Among the 147 TEAEs, 47 TEAEs were reported in 30 subjects (20.0%) receiving test product, 54 TEAEs were reported in 38 subjects (25.5%) receiving reference product and 46 TEAEs were reported in 33 subjects (22.0%) receiving placebo. Reported TEAEs were mild to moderate in severity.

<u>Conclusion</u>

- Pregabaline CNX (test product) is found superior to placebo with regards to change in mean weekly pain score from baseline to end of treatment.
- Pregabaline CNX is found non-inferior with Lyrica (reference product) with regards to change in mean weekly pain score from baseline to end of treatment.
- There was no evidence that treatment with Pregabaline CNX was associated with any significant safety risk compared to Lyrica and placebo.
- Overall, Pregabaline CNX is found to be safe, effective and tolerable in subjects with diabetic peripheral neuropathy.
- The efficacy and safety results of this trial indicate the favourable benefit/risk profile for Pregabaline CNX in patients with diabetic peripheral neuropathy. Pregabaline CNX offers an important new treatment option for these patients.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pregabaline CNX 82.5 mg, 165 mg and 330 mg.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury • Discontinuation events • Drug interactions (lorazepam, ethanol, and CNS depressants) • Euphoria • Congestive Heart Failure • Vision-related events • Abuse and drug dependence
Important potential risks	• Suicidality • Off-label use in paediatric patients
Missing information	None

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

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lyrica. The MAH demonstrated through two bioavailability studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Additionally, the MAH performed a pharmacodynamic/efficacy non-inferiority trial.
Efficacy was evaluated by change in mean weekly pain score from baseline to end of treatment. Pregabaline CNX is found superior to placebo and is found non-inferior with Lyrica (reference product) with regards to change in mean weekly pain score from baseline to end of treatment.
Safety was evaluated by incidence of treatment-emergent adverse events and serious adverse events. There was no evidence that treatment with Pregabaline CNX was associated with any significant safety risk compared to Lyrica and placebo.
Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Lyrica, EU/1/ 04/279. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pregabaline CNX 82.5 mg, 165 mg and 330 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules. Lyrica is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pregabaline CNX with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5677/001-003/IA/001	Replacement or addition of a site where batch control/testing takes place - Addition of site where batch control/testing takes place for Finished product.	No	06-06-2024	Approved	N.A.
NL/H/5677/001-003/IA/002	Updated certificate from an already approved manufacturer	No	11-07-2024	Approved	N.A.