27 February 2025
EMA/CHMP/95840/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lyrica

International non-proprietary name: Pregabalin

Procedure No. EMEA/H/C/000546/X/0127

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CHMP	Committee for Medicinal Products for Human use
CMA	Critical Material Attribute
CPP	Critical process parameter
CQA	Critical Quality Attribute
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MO	Major Objection
OD	oral dispersible
Ph. Eur.	European Pharmacopoeia
PSD	Particle Size Distribution
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QC	Quality Control
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TLC	Thin layer chromatography
TYMC	Total Combined Yeasts/Moulds Count

1. Background information on the procedure

1.1. Submission of the dossier

Upjohn EESV submitted on 27 November 2023 an extension of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (orodispersible tablet).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: N/A

The application was received by the EMA on	27 November 2023
The procedure started on	1 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 April 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 April 2024

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 May 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	12 December 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	28 January 2025
The PRAC Rapporteur's Assessment Report on the responses to the List of Outstanding Issues was circulated to all PRAC and CHMP members on	7 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 February 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lyrica on	27 February 2025

2. Scientific discussion

2.1. About the product

Lyrica (pregabalin) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg immediate-release (IR) hard capsules and 20 mg/ml oral solution are currently registered in the European Union (EU; EMEA/H/C/000546). Approved indications for Lyrica in the EU in adults are peripheral and central neuropathic pain, as adjunctive therapy for partial seizures with or without secondary generalisation, and generalised anxiety disorder. This assessment report discusses the data supporting the proposed line-extension application to the approved Lyrica marketing authorisation in the EU for an orally disintegrating tablet (ODT) formulation of strengths 25 mg, 75 mg, and 150 mg.

2.2. Quality aspects

2.2.1. Introduction

The finished product introduced with this line extension is presented as oral dispersible (OD) tablets containing 25, 75 or 150 mg of pregabalin as active substance, to facilitate the intake by patients who have difficulties to swallow the existing hard capsules.

Other ingredients are: magnesium stearate (E470b), hydrogenated castor oil, glycerol dibehenate,talc (E553b), microcrystalline cellulose (E460), D-Mannitol (E421), crospovidone (E1202), magnesium aluminometa silicate, saccharin sodium (E954), sucralose (E955), citrus flavour (flavorings, gum arabic (E414), DL-alpha-tocopherol (E307), dextrin (E1400) and isomaltulose) and sodium stearyl fumarate (E470a).

The product is available in PVC/PVDC/Aluminium blister supplied in an aluminium pouch as described in section 6.5 of the SmPC.

2.2.2. Active Substance

No new information on the active substance has been presented within this line extension application. This is acceptable since the active substance from the same manufacturer and with the same specification as the one already registered for the authorised pharmaceutical forms (hard capsules and oral solution) will be used for the manufacture of the proposed OD tablets.

The only difference is in the limit applied for particle size of the active substance, which is tighter for batches to be used to manufacture the OD tablets in comparison with the limit applied for the authorised pharmaceutical forms.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

The proposed 25 mg, 75 mg, and 150 mg OD tablets are presented as round white plain tablets debossed with "VTLY" on the top of all tablet strengths, and debossed on the bottom with "25", "75" or "150" for each of the corresponding tablet strengths.

The diameter and thickness of the OD tablets are 6.0 mm and 3.0 mm for 25 mg tablets, 8.3 mm and 4.8 mm for 75 mg tablets, and 10.5 mm and 6.0 mm for 150 mg tablets.

The appearance of the three strengths is sufficiently differentiated by dimensions and inscriptions.

The OD tablets are formulated to disintegrate rapidly in the mouth prior to swallowing.

The tablets of the three strengths are fully dose proportional and contain a high load of active substance.

Following a Major Objection (MO) from CHMP, the pharmaceutical development has been adequately described, including the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs) and Critical Material Attributes (CMAs) according to the principles of guideline ICH Q8.

The QTPP was defined as follows:

Table 1. QTTP of Lyrica OD tablets

QTPP Elements		Target
Dosage form and design		Tablet that disintegrates rapidly on the tongue prior to swallowing
Route of administration		Oral
Dosage strengths		25 mg, 75 mg and 150 mg
Pharmacokinetics		Bioequivalent to approved Lyrica IR Capsules
Stability		Meet product specification for at least 36-months at room temperature.
Drug product quality attributes	Physical appearance	Meet product specifications established based on applicable quality standards.
	Identification	
	Assay	
	Content uniformity	
	Degradation products	
	Disintegration	
Container closure system		PTP blister consisting of PVC/PVDC film and aluminium foil blister supplied in an aluminium pouch to avoid lowering of tablet hardness.
Administration/ Concurrence with labelling		Should be administered consistent with approved Lyrica IR capsules labelling.
Methods of administration		Can be swallowed with or without water.

IR: Immediate Release; PTP: Press-Through-Package; PVC: Polyvinyl chloride; PVDC: Polyvinylidene dichloride.

Various attributes of the dosage form and the product were evaluated for their impact on product CQAs that have a direct impact on safety and efficacy. These CQAs were related back to formulation and process variables. For risk management purposes, attributes that have an impact on safety and efficacy but are unlikely affected by formulation and process variables, such as appearance, identification, water content, and microbial limits were not treated as CQAs. Based on this, the following were identified as CQAs of the finished product: assay, content uniformity, degradation products, disintegration time.

Formulation and manufacturing process development were adequately discussed in the responses, including establishment of Critical Process Parameters (CPPs) and in-process controls.

The active substance is crystalline and non-hygroscopic and shows high solubility throughout the physiological pH range. It is classified as highly soluble and highly permeable compound under the Biopharmaceutical Classification System (BCS). As indicated above, the same active substance used for the existing hard capsules and oral solution is proposed to be used for the OD tablets. This was generally acceptable, but during the review, the applicant was requested to discuss whether the physical characteristics of the active substance (e.g. particle size distribution, polymorphic form, water content) can impact the specific manufacturing process of the OD tablets, and if relevant, control these characteristics in the active substance specification applied by the drug finished manufacturer, with suitably justified limits. To address this, the applicant performed studies to investigate the impact of the active substance particle size distribution on the manufacturing process and established limits for target particle size. The criticality of the parameter particle size distribution (PSD) of the active substance was confirmed by the submitted data. Other physical parameters of the active substance are not relevant or already controlled, which has been acceptably justified.

The rationale for selection of each excipient has been provided together with a justification for the selected grades of mannitol and for not testing the other excipients for functionality related characteristics. The provided discussion about selection of excipients is acceptable. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the yuzu flavour which complies with EU regulations 1334/2008 and 1333/2008. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Compatibility between pregabalin and the proposed excipients used in pregabalin granules was determined through the stability testing.

Bioequivalence of the proposed 150 mg OD tablets to the currently approved 150 mg hard capsules has been demonstrated by a bioequivalence (BE) study performed with the 150 mg strength of both products. Comparative dissolution studies have been performed between the test and reference product batches used in the BE study, on 12 units per batch, with paddle apparatus operated at 50 rpm, 900 ml medium at pH 1.2, 4.0 and 6.8 and in water. Both dosage forms, at all conditions, showed dissolution above 85% in 15 minutes. Therefore, the similarity of dissolution profiles is considered adequately demonstrated to sustain the BE study.

The applicant requested a biowaiver for the additional OD tablet strengths (25 mg and 75 mg). The three strengths are fully dose proportional and are manufactured by the same manufacturing process. Comparative dissolution profiles are provided, performed in the same conditions as described for the comparative dissolution profiles complementary to the BE study. The results were also in this case, for all batches tested in all conditions, above 85% in 15 minutes. Therefore, the similarity of dissolution profiles among strengths is considered confirmed.

It is noted that the comparative dissolution profiles have been performed at pH 1.2, 4.0 and 6.8, while the EMA Guideline on BE requires studies at pH 1.2, 4.5 and 6.8. Considering the results, with very fast dissolution in all cases, no different results are expected when testing at pH 4.5 and the submitted data is considered acceptable. Therefore, the request for a biowaiver of strength for the additional 25 mg and 75 mg strengths is considered acceptable from a pharmaceutical point of view.

An acceptable justification has been provided for replacement of a dissolution test by a disintegration test in the finished product specifications, therefore development of a quality control (QC) dissolution test method and limit are not relevant for this dossier.

The process development for the ODP tablets went through a few evolutionary prototype evaluations as part of initial formulation and process screening evaluations. These evaluations began with a prototype 1 utilizing a direct compression process then changing to a protype 2 utilizing a fluid bed granulation process to finally prototype 3 using a commercial process of dry granulation Prototype 3 that applied dry granulation demonstrated acceptable stability and showed no prominent difference in dissolution tests compared with reference capsules. Therefore, the dry granulation process was selected to develop Lyrica OD tablets.

The primary packaging is a PVC/PVDC/Aluminium blister supplied in an aluminium pouch. The material complies with Ph.Eur. and EC requirements for materials intended to come in contact with foodstuff. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product manufacturing process consists of five main steps: mixing, dry granulation, blending with extra-granular excipients, compression and packaging.

The manufacturing process and in-process controls have been described with a sufficient level of detail. Suitably justified holding times have been defined and justified by stability studies. The applicant confirmed that the shelf life of the finished product will be calculated in line with the requirements of the Note for guidance on start of shelf-life of the finished dosage form (CPMP/QWP/072/96).

The manufacturing process is considered to be standard, in view of the high active substance load and the nature of the processes applied. Major steps of the manufacturing process have been validated by a number of studies.

A MO on the originally proposed commercial batch size was raised given that the size of the batch used for the BE study and the scale of the registration batches provided to support process validation was less than 1/10 of the proposed production batch size. In response, the applicant reduced the production scales. In addition, as requested by CHMP, the applicant provided validation reports for the granulate at full scale and for the mixing and tabletting steps at maximal commercial size, on three batches for each strength. This is acceptable. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.2.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description/appearance (visual inspection), identification (TLC, HPLC), assay (HPLC), water (Ph. Eur.), degradation products, (HPLC), uniformity of dosage units-mass variation (Ph. Eur.), disintegration (Ph. Eur.), microbial limits (TAMC, TYMC, E.coli) (Ph. Eur.).

The applicant has submitted data to justify the omission of a dissolution test in the finished product specification, replaced by a disintegration test. It has been demonstrated that the disintegration test is more discriminative than a dissolution one, throughout the physiological pH range. In line with the principles of ICH Q6A decision tree #7, this is considered acceptable.

The possible organic impurities are discussed, no new impurity is formed in the finished product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches of the 75 mg strength have been tested for content of ICH Q3D Class 1, 2A, 2B and 3 elemental impurities. The results demonstrated that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory. The applicant stated that a risk evaluation on nitrosamines had been performed concluding that no nitrosamines are introduced into the product from its components, and none of the components contain any vulnerable amines capable of forming N-Nitrosamine impurities in the finished product. The detailed documentation was not provided. In line with the document "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020 most recent version), Question 19, which states that no risk evaluation is generally necessary to be submitted for line extensions and variations this was accepted and no question was raised.

Overall, the proposed finished product specification is acceptable, covering for all parameters relevant for this pharmaceutical form, with acceptable limits.

The in-house analytical methods have been adequately described and appropriately validated as per ICH Q2. The stability indicating nature of the methods for assay and related substances has been demonstrated by forced degradation studies. Suitability of the methods for microbiological quality in presence of the finished product has been demonstrated. For reference standards, reference is made to the active substance part. This is acceptable given that no new impurity is formed (and tested) in the finished product with respect to the active substance.

Batch analytical results are provided for three pilot and three production scale batches of each strength. All results comply to the specification limits. Results of microbial quality (TAMC and TYMC) testing are provided in the stability section. No results of *E. coli* is available, this test will be performed

routinely at finished product release, which is acceptable. The results provided confirm the consistency of the manufacturing process and its ability to manufacture the finished product to the proposed finished product specification.

2.2.3.4. Stability of the product

Stability data from nine batches per strength (three development, three pilot and three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

All batches were manufactured at the proposed commercial manufacturing site and were packed in the primary packaging proposed for marketing.

The parameters tested were:
-for development batches: appearance, degradation products, disintegration, dissolution, assay, water, hardness, oral disintegration test, microbiological quality;

-for pilot and production batches: appearance, assay, degradation products, disintegration and microbiological quality.

The omission of monitoring of hardness or water content has been justified.

Except for a slight increase of the specified degradation impurity (but below the shelf-life specification limit) no significant change, trend or out of specification was observed in the results of samples in the closed pouch.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, degradation products, and disintegration. A slight increase in water content and decrease of hardness were observed, but these were attributed to the tablets being outside the container (e.g. to exposure to moisture) than to the exposure to light. Therefore, the conclusion that the finished product is not sensitive to light and the storage statement 'store in the original package in order to protect from moisture' are considered acceptable.

Forced degradation studies were performed on Pregabalin OD Tablets 25mg to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and degradation products method. Since the 25, 75, and 150 mg tablet cores are made from a common blend the use of the 25 mg strength for the forced degradation studies is justified. The studies included thermal, humidity, photolysis, acid, base and oxidation studies.

An in-use study has been performed to investigate the stability of the tablets in the blisters outside the pouch. Samples were stored for 6 months at 25°C/75% RH. Water content was measured only after 6 months and showed a significant increase. Hardness was tested after 1, 2, 3 and 6 months and showed a clear decreasing trend, with results still within the hardness limits applied at in-process control stage after 3 months, but lower after 6 months. All other parameters tested (appearance, assay, degradation products, dissolution, disintegration) showed no change upon 6 months of storage outside the pouch. Based on these results, the proposed shelf life of 3 months after opening of the pouch is accepted.

[1] *6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union*

Based on available stability data, the proposed shelf-life of 3 years for the finished product stored in the original packaging and with no special temperature storage conditions, and an in-use shelf-life of 3 months after first opening of the pouch as stated in the SmPC (section 6.3) are acceptable. The warning "Store in the original packaging in order to protect from moisture" is added, which is acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the proposed OD tablets has been presented in a satisfactory manner. During the procedure 2 MO were raised by the CHMP: MO1 pertained to the insufficient level of detail provided under the pharmaceutical development section of the dossier (3.2.P.2), MO2 related to the originally proposed commercial batch size which was above 1/10 of the batch used in the BE study. To address these the applicant provided the details requested under 3.2.P.2. and reduced the commercial batch size. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application. The Applicant relied on the well-known pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin and the non-clinical dossier submitted as part of the marketing authorization applications for Lyrica® film-coated tablets. The Applicant has not provided additional studies and further studies are not required for the new orally disintegrating tablet (ODT) formulation. The proposed pregabalin ODT formulation was shown to be bioequivalent to the film-coated tablets in a pivotal bioequivalence study in human. Consequently, the need to conduct non-clinical studies to compare pharmacokinetics of the ODT versus film coated tablet is not required.

In addition to the active ingredient, Lyrica® ODT contains the following pharmaceutical excipients: D-mannitol, microcrystalline cellulosea, crospovidone, glycerin fatty acid ester, sucralose, saccharin sodium hydrate, sodium stearyl fumarate, talc, citrusa (from the Yuzu citrus plant), magnesium stearate and aluminometasilicate.

All excipients are commonly used for oral products, except for Citrus, which does not have a Ph. Eur reference and a certificate of compliance was not submitted.

2.3.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), an environmental risk assessment is required for an extension application, if there is a potential increase in the environmental exposure, e.g., because of a new route of administration. Lyrica® is approved in adults for the treatment of peripheral and central neuropathic pain, the treatment of generalized anxiety disorder and as adjunctive therapy in adults with partial seizures with or without secondary generalization.

With the present extension, the Applicant does not seek to extend the products dosage range, route of administration, posology or introduce a new therapeutic indication. Introduction of Lyrica® ODT is supposed to ease drug administration in patients, who have difficulties in swallowing the currently available hard capsules and it is assumed that Lyrica® ODT will only replace prescriptions of the currently available Lyrica® capsules in these patients. Consequently, it can be agreed that approval of the Lyrica® ODT line extension application will not lead to an increase in environmental exposure to pregabalin so that, according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), an environmental risk assessment is not required for this line extension application.

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this line extension application with regard to pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin. As pregabalin is a well-known active substance already formulated as oral hard capsule, the Applicant has not provided additional studies and further non-clinical studies are not required for the new orally disintegrating tablet (ODT) formulation.

Additional information on excipients, has been submitted. All excipients are commonly used for oral products, except for Citrus, which does not have a Ph. Eur reference and a certificate of compliance was not submitted.

Pregabalin is already used in existing marketed products and no significant increase in environmental exposure is anticipated, since the Lyrica ODT will only replace prescriptions of the currently available Lyrica capsules for patients who have difficulties in swallowing the available hard capsules. Therefore, the justification for the lack of full Environmental Risk Assessment is endorsed.

2.3.3. Conclusion on non-clinical aspects

There are no objections to approval of Lyrica ODT from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

2.4.1. Clinical pharmacology

2.4.1.1. Pharmacokinetics

The current application relies on the pharmacological (including, pharmacokinetics and pharmacodynamics) data previously established for pregabalin (Lyrica) IR formulation; no additional studies in this regard are conducted as part of this submission. This application relies on the bioequivalence study (A0081336) assessing the bioequivalence between pregabalin hard capsule 150 mg and ODT 150 mg, and a biowaiver for the additional strengths 25 mg and 75 mg.

Study A0081336 was a randomized, open-label, 3-treatment, 3-period, crossover, single-dose study. A total of twenty-four subjects were enrolled. Subjects received one of 3 treatments; pregabalin 150 mg capsule as a single oral dose under fasted conditions, pregabalin 150 mg ODT with water as a single oral dose under fasted conditions, or pregabalin 150 mg ODT without water.

All study methodology, and specifically the pharmacokinetic characterization was appropriate.

In the table below, the pharmacokinetic parameters for pregabablin, as well as the mean differences between formulations and corresponding 90% confidence intervals are presented. Mean plasma pregabalin concentration-time profiles are presented in Figure 1.

Table 2. Pharmacokinetic parameters for pregabablin (non-transformed values; arithmetic mean ± SD, tmax median, range, n=24)

Treatment	AUC_{0-t} ug/ml/h	$AUC_{0-\infty}$ ug/ml/h	C_{max} ug/ml	t_{max} h
ODT with water	31.4 ± 4.57	31.9 ± 4.73	5.79 ± 1.42	0.500 (0.33 – 1.5)
ODT no water	31.2 ± 4.97	31.7 ± 5.11	5.79 ± 1.18	1.00 (0.33 – 2.5)
Lyrica tablets	31.7 ± 4.49	32.2 ± 4.67	5.79 ± 1.23	0.875 (0.5 – 2.0)
***Ratio (90% CI) ODT with water vs tablets**	99.03 (96.75 – 101.36)		99.27 (92.85 – 106.14)	
***Ratio (90% CI) ODT no water vs tablets**	98.12 (95.86 – 100.43)		100.25 (93.77 – 107.19)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

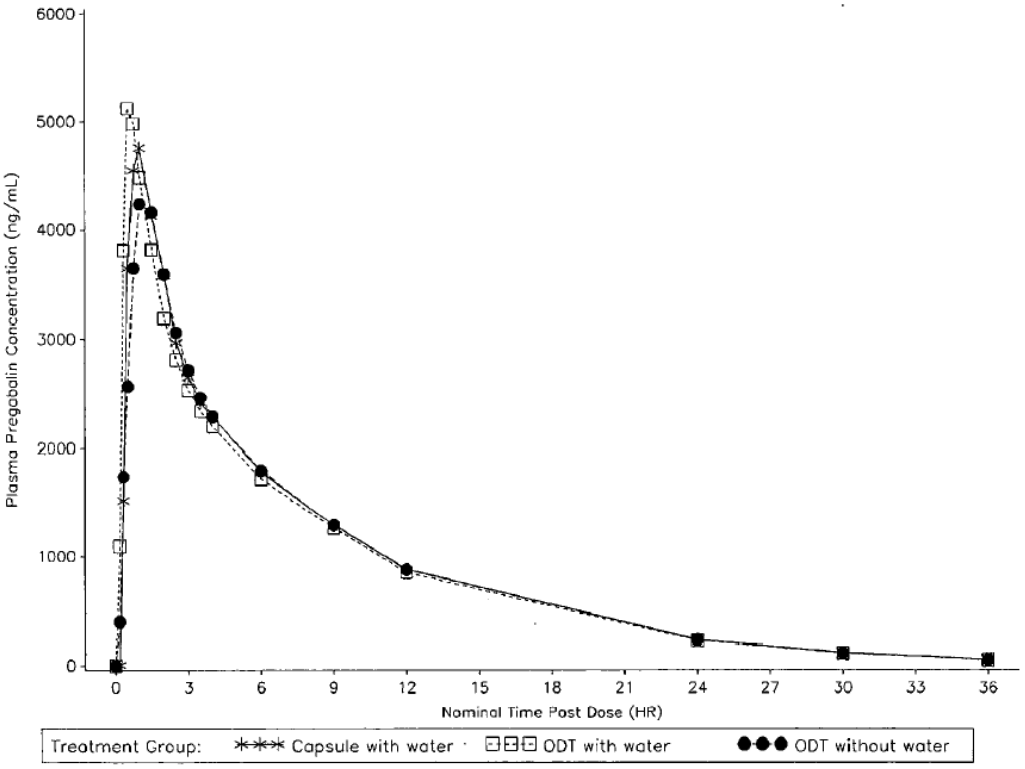

Figure 1. Mean plasma pregabalin concentration-time profiles

Bioequivalence between the different formulations has adequately been demonstrated. The pharmacokinetics have adequately been characterized and for both comparisons the 90% CIs for the ratios are within 80.00-125.00%, for both AUC_{last} and C_{max}.

2.4.2. Discussion on clinical pharmacology

Based on the submitted bioequivalence study, Pregabalin 150 mg Orally Disintegrating Tablet, Manufactured by Pfizer (Japan) is considered bioequivalent with Lyrica® (pregabalin) 150 mg capsules.

The results of study A0081336 with 150 formulation can be extrapolated to other strengths 25 and 75 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

2.4.3. Conclusions on clinical pharmacology

This line-extension can be supported from a pharmacokinetic point of view.

2.4.4. Clinical efficacy

This submission will rely on the efficacy and safety data previously established in clinical studies prior to and post MA of the pregabalin (Lyrica) IR formulation. An appropriate bioequivalence study (A0081336) was conducted to assess the equivalence following the same dose (150 mg) of the pregabalin ODT and IR formulation (hard capsule). No additional efficacy studies are conducted nor required in support of this line-extension.

2.4.5. Conclusions on clinical efficacy

The line-extension of Lyrica IR capsules to the ODT formulation does not impact the benefit risk profile.

2.4.6. Clinical safety

2.4.7. Discussion on clinical safety

The safety profile of pregabalin IR capsules has been previously established. Study A0081336 demonstrated that a single dose of pregabalin 150 mg was safe and well-tolerated regardless of dosage form administered (hard capsule, ODT with water and ODT without water). The reported AEs were mild in severity and were consistent with the known safety profile of pregabalin. There were no vital signs, ECG assessment, or safety laboratory findings considered clinically significant.

2.4.8. Conclusions on clinical safety

The line-extension of Lyrica IR capsules to the ODT formulation does not impact the benefit risk profile.

2.5. Risk management plan

The Applicant has provided an updated RMP version 14.2 with addition of the 25 mg, 75 mg, 150 mg orodispersible tablets in Part I: Product Overview, which is accepted.

2.5.1. Conclusion on the RMP

The CHMP considered that the risk management plan version 14.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Benefit risk assessment

3.1. Quality

The proposed product is approvable from a chemical-pharmaceutical point of view.

3.2. Clinical

The line-extension of Lyrica IR capsules to the ODT formulation does not impact the benefit risk profile from a clinical point-of-view. Bioequivalence has been shown for the new 150 mg ODT formulation and the existing 150 mg hard capsules, which can be extrapolated to the 25 and 75 mg strengths of the ODT.

3.3. Conclusions

The overall benefit/risk balance of Lyrica is positive, subject to the conditions stated in section 'Recommendations'

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lyrica new pharmaceutical form is favourable in the following indication(s):

Neuropathic pain
Lyrica is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy
Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised anxiety disorder
Lyrica is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Lyrica subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.