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Public Assessment Report

Name of the Product:

Naxalgan

75 mg, 150 mg, 300 mg hard capsules

(pregabalin)

Procedure number: HU/H/0504/001-003/DC

Marketing authorisation holder: Vipharm S.A.

Date: 18 May 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Naxalgan 75 mg, 150 mg and 300 mg hard capsules. The holder of the marketing authorisation is Vipharm S.A., Poland.

The active substance is pregabalin. Each hard capsule contains either 75 mg, 150 mg or 300 mg pregabalin.

The other ingredients are lactose monohydrate, maize starch, pregelatinized (maize) starch, talc, gelatine, titanium dioxide (E171) and black ink (which contains shellac, black iron oxide (E172), propylene glycol, strong ammonia solution and potassium hydroxide). The 75 mg and 300 mg capsules also contain red iron oxide (E172), and yellow iron oxide (E172)..

Appearance of Naxalgan hard capsules is as follows:
- the 75 mg strength is size no. 4, opaque white body imprinted with „75" with black ink, opaque orange cap, filled with white to off-white powder,
- the 150 mg strength is size no. 2, opaque white body imprinted with „150" with black ink, opaque white cap, filled with white to off-white powder,
- the 300 mg strength is size no. 0, opaque white body imprinted with „300" with black ink, opaque orange cap, filled with white to off-white powder.

They are available in carton pack of PVC/PE/PVdC/Aluminium Blister or in HDPE bottle with white polypropylene, round plastic child-resistant tamper-evident screw cap with a liner for induction sealing.

Naxalgan hard capsules (further on: Naxalgan) belong to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD) in adults.

Peripheral and central neuropathic pain: Naxalgan is used to treat long lasting pain caused by damage to the nerves. A variety of diseases can cause peripheral neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles. Peripheral and central neuropathic pain may also be associated with mood changes, sleep disturbance, fatigue (tiredness), and can have an impact on physical and social functioning and overall quality of life.

Epilepsy**:** Naxalgan is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation) in adults. The doctor will prescribe it for the patients to help treating of their epilepsy when the current treatment is not controlling their condition. Patients should take Naxalgan in addition to their current treatment. Naxalgan is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder**:** Naxalgan is used to treat GAD. The symptoms of GAD are prolonged excessive anxiety and worry that are difficult to control. GAD can also cause restlessness or feeling keyed up or on edge, being easily fatigued (tired), having difficulty concentrating or mind going blank, feeling irritable, having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.

What patients need to know before taking Naxalgan

Those who are allergic to pregabalin or any of the other ingredients of this medicine, *must not take Naxalgan*.

Warnings and precautions

- Some patients taking pregabalin have reported symptoms suggesting an allergic reaction. These symptoms include swelling of the face, lips, tongue, and throat, as well as diffuse skin rash. Should the patient experience any of these reactions, he/she should contact the physician immediately.
- Pregabalin has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Therefore, patients should be careful until they are used to any effect the medicine might have.
- Pregabalin may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary. Patients should immediately tell their doctor if experiencing any changes in their vision.
- Some patients with diabetes who gain weight while taking pregabalin may need an alteration in their diabetic medicines.
- Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to pregabalin and the severity of these effects may be increased when taken together.
- There have been reports of heart failure in some patients when taking pregabalin; these patients were mostly elderly with cardiovascular conditions. Before taking this medicine patients should tell their doctor if they have a history of heart disease.
- There have been reports of kidney failure in some patients when taking pregabalin. If while taking pregabalin patients notice decreased urination, they should tell it their doctor as stopping the medicine may improve this.
- A small number of people being treated with anti-epileptics such as pregabalin have had thoughts of harming or killing themselves. If at any time a patient havs these thoughts, he/she must immediately contact the doctor.
- When pregabalin is taken with other medicines that may cause constipation (such as some types of pain medicines) it is possible that gastrointestinal problems may occur (e.g. constipation, blocked or paralysed bowel). Patients should tell their doctor if experiencing constipation, especially if they are prone to this problem.
- Before taking this medicine patients should tell their doctor if they have a history of alcoholism or any drug abuse or dependence. Pateints should not take more medicine than prescribed.

- There have been reports of convulsions when taking pregabalin or shortly after stopping pregabalin. Those who experience a convulsion, contact their doctor immediately.
- There have been reports of reduction in brain function (encephalopathy) in some patients taking pregabalin when they have other conditions. Those who have a history of any serious medical conditions, including liver or kidney disease, tell it to their doctor.

Children and adolescents

The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, pregabalin should not be used in this age group.

Other medicines and Naxalgan

Patients must tell their doctor if they are taking, have recently taken or might take any other medicines.

Pregabalin and certain other medicines may influence each other (interaction). When taken with certain other medicines, pregabalin may potentiate the side effects seen with these medicines, including respiratory failure and coma. The degree of dizziness, sleepiness and decreased concentration may be increased if pregabalin is taken together with medicines containing:
- oxycodone – (used as a pain-killer),
- lorazepam – (used for treating anxiety),
- alcohol.

Naxalgan may be taken with oral contraceptives.

Naxalgan with food, drink and alcohol

Naxalgan may be taken with or without food. However, it is advised not to drink alcohol while taking Naxalgan.

Pregnancy and breast-feeding

Pregabalin should not be taken during pregnancy or when breast-feeding, unless the patient is told otherwise by her doctor. Effective contraception must be used by women of child-bearing potential. Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Driving and using machines

Pregabalin may produce dizziness, sleepiness and decreased concentration. Patients should not drive, operate complex machinery or engage in other potentially hazardous activities until they know whether this medicine affects their ability to perform these activities.

Naxalgan contains lactose monohydrate

Those who have been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicine.

How to take Naxalgan

Patients must always take this medicine exactly as the doctor prescribed. The doctor will determine what dose is appropriate for a given patient.

Naxalgan is for oral use only.

Peripheral and central neuropathic pain, epilepsy or Generalised Anxiety Disorder:
- The patient must take the number of capsules as instructed by his/her doctor.
- The dose, which has been adjusted for the patient and the patient's condition, will generally be between 150 mg and 600 mg each day.
- The doctor will tell the patient to take Naxalgan either twice or three times a day. For twice a day, the patient takes Naxalgan once in the morning and once in the evening, at about the same time each day. For three times a day the patient takes Naxalgan once in the morning, once in the afternoon and once in the evening, at about the same time each day.

If the patient havs the impression that the effect of Naxalgan is too strong or too weak, consult it with the doctor.

Elderly patients (over 65 years of age) should take Naxalgan normally except if they have problems with the kidneys.

The doctor may prescribe a different dosing schedule and/or dose if you have problems with the kidneys.

The capsule should be swallowed whole with water.

Patients should continue taking Naxalgan until the doctor tells them to stop it.

What to do if more Naxalgan has been taken than it should have been?

The doctor or the nearest hospital emergency unit must be visited immediately. The box or bottle of Naxalgan must be carried. Patients may feel sleepy, confused, agitated, or restless as a result of taking more Naxalgan than they should. Fits have also been reported.

What to do if taking Naxalgan has bee forgotten?

It is important to take the Naxalgan regularly at the same time each day. If taking a dose has been forgotten, it should be taken as soon as remembering it unless it is time for the next dose. In that case, patients should just carry on with the next dose as normal. They should never take a double dose to make up for a forgotten dose.

May patients stop taking Naxalgan?

Patients should not stop taking Naxalgan unless their doctor tells them to. If the treatment is stopped it should be done gradually over a minimum of 1 week.

After stopping long and short-term pregabalin treatment, patients need to know that they may experience certain side effects. These include, trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flulike symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. These symptoms may occur more commonly or severely if the patient has been taking pregabalin for a longer period of time.

Possible side effects

Like all medicines, Naxalgan can cause side effects, although not everybody experiences them.

Very common: may affect more than 1 in 10 people: dizziness, drowsiness, headache.

Common: may affect up to 1 in 10 people
- increased appetite,
- feeling of elation, confusion, disorientation, decrease in sexual interest, irritability,
- disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal,
- blurred vision, double vision,
- vertigo, problems with balance, fall,
- dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen,
- difficulties with erection,
- swelling of the body including extremities,
- feeling drunk, abnormal style of walking,
- weight gain,
- muscle cramp, joint pain, back pain, pain in limb,
- sore throat.

Uncommon: may affect up to 1 in 100 people
- loss of appetite, weight loss, low blood sugar, high blood sugar,
- change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attack, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation,
- changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell,
- dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.

- heart rhythm disturbances, increased heart rate, low blood pressure, high blood pressure, changes in heart beat, heart failure,
- flushing, hot flushes,
- difficulty breathing, dry nose, nasal congestion,
- increased saliva production, heartburn, numb around mouth,
- sweating, rash, chills, fever,
- muscle twitching, joint swelling, muscle stiffness, pain including muscle pain, neck pain,
- breast pain,
- difficulty with or painful urination, incontinence,
- weakness, thirst, chest tightness,
- changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate aminotransferase increased, platelet count decreased, neutropaenia, increase in blood creatinine, decrease in blood potassium),
- hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring,
- painful menstrual periods,
- coldness of hands and feet.

Rare: may affect up to 1 in 1,000 people
- abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss,
- dilated pupils, cross eyes,
- cold sweat, tightness of the throat, swollen tongue,
- inflammation of the pancreas,
- difficulty in swallowing,
- slow or reduced movement of the body,
- difficulty with writing properly,
- increased fluid in the abdomen,
- fluid in the lungs,
- convulsions,
- changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances,
- muscle damage,
- breast discharge, abnormal breast growth, breast growth in males,
- interrupted menstrual periods,
- kidney failure, reduced urine volume, urinary retention,
- decrease in white blood cell count,
- inappropriate behaviour,
- allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain),
- jaundice (yellowing of the skin and eyes).

Very rare: may affect up to 1 in 10,000 people
- liver failure,
- hepatitis (inflammation of the liver).

Those who experience swollen face or tongue or if the skin turns red and starts to blister or peel, should seek immediate medical advice.

Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to pregabalin and the severity of these effects may be increased when taken together.

How to store Naxalgan

This medicine does not require any special storage conditions but it should be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Naxalgan 75 mg, 150 mg and 300 mg hard capsules. The procedure was finalised at 15 February 2018. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: the Czech Republic, Poland and the Slovak Republic) concerned the generic version of pregabalin 75 mg, 150 mg and 300 mg hard capsules (Naxalgan capsules).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore, except for demonstrating bioequivalence, contained no new clinical or preclinical data, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator (and reference) products were Lyrica 75 mg, 150 mg and 300 mg hard capsules marketed by Pfizer Ltd, approved for more than 10 years. Since the marketing authorisation was granted the range of indications has widened. As the license for the products was issued before 2005, on the basis Article 89 of the Directive 726/2004/EC data exclusivity is 10 years and is not extended, the data protection period is already expired.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Naxalgan 75 mg, 150 mg and 300 mg hard capsules from Vipharm S.A., Poland.

The products are indicated for the treatment of peripheral and central neuropathic pain in adults, in epilepsy as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of Generalised Anxiety Disorder (GAD) in adults.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

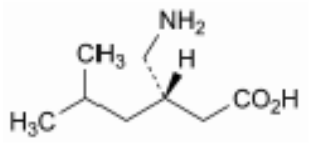
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Naxalgan 75 mg, 150 mg and 300 mg hard capsules via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). Reference products are Lyrica 75, 150 and 300 mg hard capsules (containing pregabalin as active ingredient) which were the original products of Pfizer.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Ph. Eur. name: pregabalin
Chemical name: (3S)-3-(Aminomethyl)-5-methylhexanoic acid;
(S)-(+)-4-amino-3-(2-methylpropyl) butanoic acid;
(S)-(+)-3-isobutyl-γ-aminobutyric acid
Structure:



The drug substance is white or almost white crystalline powder, sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane, isopropanol and acetone. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance complies with the requirements on genotoxic impurities.

The drug substance is specified according to the requirements of the current Ph. Eur. monograph, additional specifications have been set for residual solvents as well as for microbiological purity and for particle size.

The Ph. Eur. specification includes the following tests for pregabalin: appearance, identification by IR and HPLC, enantiomeric purity, related substances, water content, sulphated ash, and assay.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period of 3 years and the packaging material (polyethylene bag in an aluminium/polyethylene bag placed in a fibre drum) have been mentioned in the CEPs.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop hard capsules containing pregabalin as drug substance in 75, 150 and 300 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Lyrica 75, 150 and 300 mg capsules, the branded original products of Pfizer.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

> The 75 mg hard capsules: hard gelatin capsules, size no. 4, opaque white body imprinted with „75” with black ink, opaque orange cap, filled with white to off-white powder.
>
> The 150 mg hard capsules: hard gelatin capsules, size no. 2, opaque white body imprinted with "150" with black ink, opaque white cap, filled with white to off-white powder-
>
> The 300 mg hard capsules: hard gelatin capsules, size no. 0, opaque white body imprinted with "300" with black ink, opaque orange cap, filled with white to off-white powder.

The excipients used in the finished product are lactose monohydrate, maize starch, pregelatinised maize starch, and talc in the filling, and gelatin, titanium dioxide, red and yellow iron oxides (the latter two for 75 and 300 mg capsules) in the capsule shell. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificate of analysis for the batch involved in the bioequivalence study is presented.

The container closure systems of the product are PVdC/PE/PVC//Al blisters or HDPE containers consisting of white opaque HDPE bottle with white polypropylene, round plastic child-resistant tamper-evident screw cap with a liner for induction sealing. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved, as well as an in-use shelf life of 98 days with the storage conditions specified as “The drug product does not require any special storage conditions” for HDPE containers.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, no further studies are required, and the applicant provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, pregabalin. Overview based on literature review is appropriate.

III.2 Pharmacology

The drug product Naxalgan hard capsules contains the active substance pregabalin, which is a gamma-aminobutyric acid analogue. Its efficacy in the treatment of neuropathic pain, generalized anxiety disorder and epilepsy results from its binding to the alpha-2-delta subunit associated with voltage-gated calcium channels in the central nervous system. Potent binding at this site reduces calcium influx at nerve terminals and, therefore, reduces the release of several neurotransmitters, including glutamate, noradrenaline (norepinephrine) and substance P. These effects result in analgesic, anxiolytic, and anticonvulsant activity.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of pregabalin.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Published information on toxicological studies with pregabalin was the basis for the evaluation. No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

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

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of pregabalin are well-known. As Naxalgan is a generic product there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of pregabalin is well known.

Except for demonstrating bioequivalence no new non-clinical pharmacokinetic studies were conducted by the Applicant as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Pregabalin is rapidly and well absorbed, with peak plasma concentrations occurring within 0.7-1.3 hours following both single and multiple dose administration. Following repeated administration, steady state is achieved within 24 to 48 hours. The absolute oral bioavailability of the hard capsule formulation is approximately 90%. Administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption, and there is no effect of a high fat meal on the bioavailability of pregabalin.

Pregabalin has an estimated volume of distribution of 0.56 L/kg, suggesting that is predominantly distributed throughout total body water. This is consistent with its high water-solubility and negligible plasma protein binding.

Pregabalin undergoes negligible metabolism in humans. Following an orally administered dose of radiolabelled pregabalin, less than 0.1 % was recovered in the faeces and 98% of the
radioactivity recovered in the urine was unchanged pregabalin.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Renal function is an important determinant of pregabalin elimination. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

IV.2.2 Bioequivalence study

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product (Naxalgan 300 mg hard capsules) and the reference product Lyrica® 300 mg hard capsules (Pfizer), according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/ Rev 1/Corr** 2010*).

It was a randomized, crossover bioequivalence study after single administration to healthy volunteers under fasting conditions.

The study was conducted in compliance with the requirements of guideline on *Good Clinical Practice, ICH Topic E6* (*CPMP/ICH/135/95*), and *Guideline on the investigation of bioequivalence* (*CPMP/EWP/QWP/1401/98)* and ethical principles stated of the *Declaration of Helsinki (Tokyo, 2004).*

Determination of pregabalin in plasma samples was performed using an LC-MS/MS method.

Statistical methods used in the evaluation of bioequivalence were as follows.BE
- descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for Test- and Reference pharmacokinetic,
- log-transformation of AUC_{0-t} and C_{max} data,
- calculation of 90% confidence intervals for the difference between the least square means for primary parameters at $\alpha = 0.05$ significance level,
- applying non-parametric analysis of T_{max} on untransformed data
- descriptive statistics of safety data collected during the whole study period.

Bioequivalence criteria: the test product can be considered bioequivalent to the Reference product, when the ln-transformed Test/Reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00% for pregabalin.

The results are shown in the Table below.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference %	Confidence Interval	CV%
AUC_{0-t}	100.06	98.22 – 101.91%	4,27
C_{max}	99.38	93.003 – 106.15%	15.36

This study has demonstrated that a single dose of applicant's pregabalin 300 mg hard-capsules (manufactured by Vipharm S.A., Poland) was bioequivalent to a single dose of Lyrica 300 mg hard capsules (pregabalin) (manufactured by Pfizer Ltd, UK) in healthy adult subjects under fasting conditions.

No death, serious or life-threatening adverse events occurred during the study. No new safety concern was identified.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 70 mg and 150 mg on the basis of general biowaiver requirements.

- Qualitative compositions of the claimed strengths (75 and 150 mg) are the same.
- Quantitative compositions of the claimed strengths are proportionally similar.
- Based on results of comparative dissolution test, similarity of dissolution profiles of the developed three dose-strength products (75 mg, 150 mg and 300 mg) was justified according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).

Thus, the results of the bioequivalence study with 300 mg formulation can be extrapolated to other strengths 75 mg and 150 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence study and the biowaiver evaluation, Naxalgan 75 mg, 150 mg and 300 mg hard capsules are is considered bioequivalent with Lyrica 75 mg, 150 mg and 300 mg hard capsules.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of Naxalgan 75 mg, 150 mg, 300 mg hard capsules and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of pregabalin.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted, and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of pregabalin.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Pharmacovigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• Weight gain. • Peripheral oedema and oedema related events. • Dizziness, Somnolence, Loss of Consciousness, Syncope and Potential for Accidental Injury. • Discontinuation Events. • Drug interactions (lorazepam, ethanol, and CNS depressants). • Euphoria. • Hypersensitivity and allergic reactions. • Congestive heart failure. • Vision-related events. • Abuse, misuse and dependence.
Important potential risks	• Suicidality. • Haemangiosarcoma. • Off-label use in paediatric patients.
Missing information	• Pregnant and lactating women.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Naxalgan 75 mg, 150 mg and 300 mg hard capsules. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Naxalgan 75 mg, 150 mg and 300 mg hard capsules. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products 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.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on humans. For these applications the bioequivalence studies described in section IV.2 are pivotal.

To support the application, the applicant has adequately demonstrated bioequivalence between Naxalgan 75 mg, 150 mg and 300 mg hard capsules and Lyrica 75 mg, 150 mg and 300 mg hard capsules.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Naxalgan 75 mg, 150 mg and 300 mg hard capsules, generic versions of pregabalin. The applicant and the future holder of authorisation is Vipharm S.A., Poland.

Naxalgan is indicated in adults for the treatment of peripheral and central neuropathic pain, generalized anxiety disorder, and in epilepsy as adjunctive therapy in patients with partial seizures with or without secondary generalization.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Lyrica 75 mg, 150 mg and 300 mg hard capsules (Pfizer).

To support the application the applicant has adequately demonstrated bioequivalence between the test- and reference products. Moreover, the application contains an adequate review of published clinical data.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Naxalgan 75 mg, 150 mg and 300 mg hard capsules

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number HU/H/0504/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IB B.II.f.1.b.1 Extension of shelf-life of the medicinal product as packaged for sale from 2 years to 3 years	001-003/001	yes	17. 10. 2019	16. 11. 2019	approval	no