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Public Assessment Report

Name of the Product:

Rabakir

25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg hard capsules

(pregabalin)

Procedure number: HU/H/0378/001-007/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 16 September 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Rabakir 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules. The holder of the marketing authorisation is Gedeon Richter Plc in Bulgaria, Czech Republic, Estonia, Hungary, Croatia, Lithuania, Latvia and Slovakia, Gedeon Richter Romania S.A. in Romania and Gedeon Richter Polska Sp. z. o.o. in Poland.

The active substance is pregabalin. Each hard capsule contains either 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg or 300 mg pregabalin.

The other ingredients are: lactose monohydrate, pregelatinised maize starch, maize starch, talc. The capsule shell contains: gelatine, titanium dioxide (E171), quinoline yellow (E104), sunset yellow FCF-FD&C Yellow 6 (E110), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172) as indicated in the following table:

Components of the capsule shells	*Strengths*
gelatine	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules
titanium dioxide (E171)	25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 200 mg hard capsules
quinoline yellow (E104)	25 mg, 50 mg, 100 mg and 200 hard capsules
sunset yellow FCF-FD&C Yellow 6 (E110)	25 mg, 50 mg, 100 mg and 200 hard capsules
yellow iron oxide (E172)	50 mg, 75 mg, 100 mg and 150 mg hard capsules
red iron oxide (E172)	50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules
black iron oxide (E172)	50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules

The appearance of the Rabakir hard capsules is as follows.

Strength	*Appearance*
25 mg	Yellow cap and yellow body without any marking. Capsule size: No. 4 Coni-Snap.
50 mg	Light brown cap and yellow body without any marking. Capsule size: No. 3 Coni-Snap.

75 mg	Light brown cap and light brown body without any marking. Capsule size: No. 4 Coni-Snap.
100 mg	Brown cap and yellow body without any marking. Capsule size: No. 3 Coni-Snap.
150 mg	Brown cap and brown body without any marking. Capsule size: No. 2 Coni-Snap.
200 mg	Dark brown cap and yellow body without any marking. Capsule size: No. 1 Coni-Snap.
300 mg	Dark brown cap and dark brown body without any marking. Capsule size: No. 0 Coni-Snap.

The hard capsules are packaged in transparent PVC-Alu blisters, packed into folded carton box with a patient leaflet.

Rabakir belongs to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD) in adults.

Peripheral and central neuropathic pain: Rabakir 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: Rabakir is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation) in adults. The doctor will prescribe it to help treating the epilepsy when the current treatment is not controlling the condition. Thus, Rabakir should be taken in addition to the current treatment. Rabakir is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder: Rabakir 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, and having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.

What patients need to know before taking Rabakir?

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

Warnings and precautions

Patients should consult their doctor before taking Rabakir.

- Some patients taking Rabakir 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.
- Rabakir 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 having been used to any effect the medicine might have.
- Rabakir may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary. When experiencing any changes in the vision the patient must consult the doctor immediately.
- 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 the patient should inform the doctor if having a history of heart disease.
- There have been reports of kidney failure in some patients when taking pregabalin. If while taking Rabakir the patient notices decreased urination, it should be told the doctor as stopping the medicine may improve this.
- A small number of people being treated with anti-epileptics such as Rabakir have had thoughts of harming or killing themselves. If at any time the patient has these thoughts, the doctor must be contacted immediately.
- When Rabakir 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). Those who experience constipation, especially if the patient is prone to this problem, should discuss it with the doctor.
- Before taking this medicine the patient should tell the doctor if having a history of alcoholism or any drug abuse or dependence. Patients should not take more medicine than prescribed.
- There have been reports of convulsions when taking pregabalin or shortly after stopping it. If a patient experiences a convulsion, the doctor should be contacted immediately.
- There have been reports of reduction in brain function (encephalopathy) in some patients taking pregabalin when they have other conditions. Those who you have a history of any serious medical conditions, including liver or kidney disease, must inform their doctor accordingly.

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 Rabakir

Those who are taking, have recently taken or might take any other medicines, tell it their doctor. Rabakir and certain other medicines may influence each other (interaction). When taken with certain other medicines, Rabakir 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 Rabakir is taken together with medicinal products containing:

- oxycodone – (used as a pain-killer),
- lorazepam – (used for treating anxiety).
- alcohol.

Rabakir may be taken with oral contraceptives.

Rabakir with food, drink and alcohol

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

Pregnancy and breast-feeding

Rabakir should not be taken during pregnancy or when breast feeding, unless it is told otherwise by the 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

Rabakir 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.

Rabakir contains lactose monohydrate and sunset yellow (E110)

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

Rabakir 25 mg, 50 mg, 100 mg and 200 mg hard capsules contain Sunset yellow FCF – FD&C Yellow 6 (E110). Sunset yellow may cause allergic reactions.

How to take Rabakir?

Rabakir is for oral use only.

The doctor will determine what dose is appropriate for the given patient.

General advices for patients suffering in peripheral and central neuropathic pain, epilepsy or Generalised Anxiety Disorder:

- take the number of capsules as instructed by your doctor;

- the dose, which has been adjusted for you and your condition, will generally be between 150 mg and 600 mg each day;
- Your doctor will tell you to take Rabakir either twice or three times a day. For twice a day take Rabakir once in the morning and once in the evening, at about the same time each day. For three times a day take Rabakir once in the morning, once in the afternoon and once in the evening, at about the same time each day.

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

The doctor may prescribe a different dosing schedule and/or dose for those who have problems with the kidneys.

The capsule should be swallowed whole with water.

Taking Rabakir must be continued until the doctor tells to stop.

What to do if more Rabakir has been taken than it should be?

The doctor or the nearest hospital emergency unit must be contacted immediately. The box of Rabakir should be presented. The patient may feel sleepy, confused, agitated, or restless as a result of taking more Rabakir than it should be.

What to do if taking Rabakir was forgotten?

It is important to take the Rabakir capsules regularly at the same time each day. If taking a dose has been forgotten, it should be taken as soon as the patient remembers unless it is time for the next dose. In that case, the patient only needs just carry on with the next dose as normal. Double dose should not be taken to make up for a forgotten dose.

How to stop taking Rabakir?

Taking Rabakir should not be stopped unless the doctor tells it to. If the treatment is stopped it should be done gradually over a minimum of 1 week.

After stopping long and short-term Rabakir treatment, the patient needs to know that certain side-effects may be experienced. These include trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flu-like symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. These symptoms may occur more commonly or severely if Rabakir have been taken for a longer period of time.

Possible side-effects

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

Very common side-effects which may affect more than 1 person in 10 are: dizziness, drowsiness and headache.

Common side-effects which may affect more than 1 person in 100 are listed below:
- 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 side-effects which may affect more than 1 person in 1000 are listed below:
- 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 attacks, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase of 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 heartbeat, 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, neutropenia, 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 side-effects which may affect less than 1 person in 1000 are listed below**:**

- 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).

If the patient experiences swollen face or tongue or if the skin turns red and starts to blister or peel immediate medical advice must be sought.

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

How to store Rabakir?

This medicinal product does not require any special storage conditions but keep it out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Rabakir 25 mg, 50 mg, 75 mg, 100 mg, 1540 mg, 200 mg and 300 mg hard capsules. The procedure was finalised at 25 July 2015. 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 applications (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Croatia, the Czech Republic, Estonia, Latvia, Lithuania, Poland, Romania and the Slovak Republic) concerned the generic versions of pregabalin 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Rabakir 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules of Gedeon Richter Plc.

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 (SmPC).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has claimed BCS-based biowaiver for all strengths.

The originator products are Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 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 been widened. As the license for the products was issued before November 2005, on the basis of Art. 89 of the Directive 726/2004/EC data exclusivity is 10 years and is not extended. Thus, the data protection period has already been expired in the European Economic Area.

II. QUALITY ASPECTS

II.1 Introduction

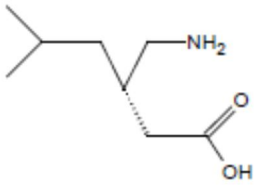
This chemical-pharmaceutical assessment report concerns the application of Rabakir 25, 50, 75, 100, 150, 200 and 300 mg hard capsules via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (generic application). The products have been developed by Gedeon Richter Plc.

The reference products are Lyrica hard capsules (containing 25, 50, 75, 100, 150, 200, 300 mg 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 Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: pregabalin
Chemical name: S-(+)-3-(aminomethyl)-5-methylhexanoic acid
Structure:



The active substance is white, almost white powder. It is soluble in acetic acid, sparingly soluble in water, slightly soluble in methanol and very slightly soluble in dichloromethane, acetonitrile, acetone and isopropyl alcohol.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by ^{1}H and ^{13}C-NMR spectra, CNH analysis, mass spectra and FT-IR spectra. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Pregabalin is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the active substance, which includes the following tests: characters, particle size, identification, achiral test, chiral test, tartaric acid content, palladium content, sulphated ash, loss on drying, heavy metals, assay, residual solvents and microbial examination.

Testing methods are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

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

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable with "Store in the original packaging protected from light" storage condition, in PE bags.

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

II.3 Medicinal product

The aim was to develop film-coated tablets containing pregabalin.as drug substance in 25, 50, 75, 100, 150, 200, 300 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Lyrica 25, 50, 75, 100, 150, 200, 300 mg film-coated tablets, 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 products are is shown to be similar to the reference products.

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.

- 25 mg hard capsules: yellow shell cap and yellow shell body without any marking, size 4.
- 50 mg hard capsules: light brown shell cap and yellow shell body without any marking, size 3.
- 75 mg hard capsules: light brown shell cap and light brown shell body without any marking, size 4.
- 100 mg hard capsules: brown shell cap and yellow shell body without any marking, size 3.
- 150 mg hard capsules: brown shell cap and brown shell body without any marking, size 2.
- 200 mg hard capsules: dark brown shell cap and yellow shell body without any marking, size 1.
- 300 mg hard capsules: dark brown shell cap and dark brown shell body without any marking, size 0.

The capsules are packaged in blisters made of transparent hard PVC blister foil and hard aluminium foil of sufficient pharmaceutical quality.

The excipients used in the finished product are lactose monohydrate, starch pregelatinised maize), maize starch, talc, gelatin, iron oxide red, iron oxide black, iron oxide yellow, titanium dioxide, quinolone yellow sunset yellow. All excipients, except the colorants, 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 Conference on 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.

The container closure system of the product is transparent PVC//Al blister. 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 3 years with no special storage conditions is approved.

The Summary of Product Characteristics, patient Information 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 quality aspects 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 non-clinical studies are required and the applicant has 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 for this application.

III.2 Pharmacology

The drug product Rabakir contains the active substance pregabalin, which is a gamma-amino-butyric acid analogue: (S)-3-(aminomethyl)-5-methylhexanoic acid. 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 activities.

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

Since Rabakir 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 Rabakir 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.

No specific clinical studies had been performed, as the application has been submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended. The application contains an adequate review of published clinical data.

The applicant requested BSC-based biowaiver for all strengths of Rabakir hard capsules on the basis of the characteristics of active substance and in line with the *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/rev 1/Corr**, Appendix III, 2010)* as supporting data for claiming essential similarity to reference products Lyrica hard capsules.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption/distribution: pregabalin is rapidly and well absorbed, with peak plasma concentrations occurring within 0.7-1.3 hours after dosing. . 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.

Biotransformation and elimination: 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. The mean elimination half-life is 6.3 hours. Renal function is an important determinant of pregabalin elimination. The plasma clearance and renal clearance are directly proportional to creatinine clearance.

IV.2.2 Bioequivalence

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

Biowaiver

The applicant claimed for BCS-based biowaiver for the 25 mg, 50 mg, 75 mg, 100 mg,

150 mg, 200 mg and 300 mg dose (all) strengths. Criteria relating to BCS-based biowaiver are met for each dose strength (25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg) of the test product, according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr**, Appendix III, 2010*).

These BCS-based biowaiver criteria are as follows:

- The drug substance pregabalin has been proven to exhibit high solubility and high absorption (BCS class I).
- Very rapid (> 85 % within 15 min) *in vitro* dissolution characteristics of the test (pregabalin 25, 50, 75, 100, 150, 200, 300 mg, hard capsules; manufactured by Gedeon Richter Plc.) and reference product (Lyrica capsules, 25, 50, 75, 100, 150, 200 and 300 mg pregabalin; manufactured/marketed by Pfizer Deutschland GmbH) has been demonstrated considering specific requirements.
- Excipients of the test and reference products do not affect the bioavailability of the active substance**.**

In addition, it is written in the *Scientific Discussion for approval of Lyrica (EMEA, 2004)* that pregabalin meets the criteria of a biowaiver application as required by above cited EMA Guideline.

The biowaiver claim for the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg dose strengths is therefore justified as the general requirements for biowaiver are completely fulfilled.

Conclusion on bioequivalence: the justification for BCS (Biopharmaceutical Classification System) based biowaiver can be accepted. All corresponding strengths of the reference Lyrica hard capsules and the Rabakir hard capsules are considered bioequivalent.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics Rabakir 25mg, 50mg, 75mg, 100mg, 150mg, 200 mg, 300 mg hard capsules were not performed and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy or safety 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

No new safety data were submitted and none were required for this application. 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 new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice (GVP) module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury Hypersensitivity and allergic reactions Vision-related events Peripheral (oedema) and Oedema-related events Discontinuation events Drug interactions (lorazepam, ethanol and CNS depressants) Euphoria Weight gain Congestive heart failure Drug dependence, misuse and abuse
Important potential risks	Haemangiosarcoma Suicidality Off-label use in children and adolescents
Missing information	Use during pregnancy and breast-feeding

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to products of pregabalin 25mg, 50mg, 75mg, 100mg, 150mg, 200 mg, 300 mg hard capsules of Gedeon Richter Plc. No additional activities are proposed and needed.

Routine risk minimisation measures (i.e. wording in the SmPC, package leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to the products. No additional activities are proposed and needed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports (PSURs) 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.

According to the latest EURD list (16 July 2015, EMA/630645/2012 Rev.32) PSUR for pregabalin should be submitted annually, the last Data Lock Point was 2015.01.31. PSURs are required for products referred to in Article 10(1) as well, so the applicant has to submit PSURs.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence described in section IV.2 is pivotal.

No formal clinical trial (bioequivalence study) had been carried out on the products Rabakir 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 300 mg hard capsules manufactured by Gedeon Richter Plc. as BCS-based biowaiver has been requested for them on the basis of the characteristics of active substance and in line with the Guideline on the investigation of bioequivalence (*CPMP/EWP/QWP/1401/ 98/rev 1/Corr**, Appendix III, 2010*).

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 Rabakir 25 mg, 50 mg, 75 mg, 10 mg, 150 mg, 200 mg and 300 mg hard capsules, generic versions of pregabalin. The applicant and the future holder of authorisation is Gedeon Richter Plc in Bulgaria, Czech Republic, Estonia, Hungary, Croatia, Lithuania, Latvia and Slovakia, Gedeon Richter Romania S.A. in Romania and Gedeon Richter Polska Sp. z. o.o. in Poland.

Rabakir 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 products were Lyrica hard capsules of the same strengths (Pfizer). To support the application the applicant has adequately justified the BCS-based biowaiver for all dose strengths on the basis of the bioequivalence guideline in force (*Appendix III, CPMP/EWP/QWP/1401/98/rev 1/Corr***).

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 Rabakir 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 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 Hungarian.

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	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached