LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Brieka
(pregabalin)

SE/H/1399/01-08/DC

This module reflects the scientific discussion for the approval of Brieka. The procedure was finalised on 2015-06-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The applications for Brieka, 25, 50, 75, 100, 150, 200, 225 and 300 mg, capsules, hard, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BG, CY, CZ, DK, EE, EL, FI, HR, HU, IE, IS, LT, LV, MT, PL, RO, SI, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is LYRICA, 25; 50; 75; 100; 150; 200; 225 and 300 mg, capsules, hard, authorised in the EU since 2004, with Pfizer Ltd. as marketing authorisation holder. The reference product used in the bioequivalence study is LYRICA, 50 mg and 300 mg, capsules, hard, from the UK with Pfizer Ltd., as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pregabalin has an oral bioavailability of ≥90 % independent of dose. Following an oral dose of pregabalin maximal plasma concentrations occur within one hour. The rate of pregabalin absorption is decreased when given with food but the extent of absorption is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. The pharmacokinetics of pregabalin is linear over the recommended daily dose range. The terminal half-life is 6.3 hours. Pregabalin is eliminated primarily by renal excretion as unchanged drug.

Bioequivalence was evaluated in two single-dose, two-way crossover studies in the fasted state with the 300 mg and the 50 mg strengths respectively, since the two lowest strengths 25 and 50 mg are not dose-proportional to the higher strengths. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of pregabalin were determined with an adequately validated LC/MS/MS method. The use of conventional acceptance limits is acceptable since the recommended dose range is wide (150 mg/day – 600 mg/day) and the risks associated with a potentially small increase in exposure above the highest recommended exposure of the originator seems negligible. Therefore, pregabalin is not considered to have a narrow therapeutic index.

Study 2353/11 was conducted in 32 healthy volunteers and compared Pregabalin, 50 mg, capsules with Lyrica, 50 mg, hard capsules. The study was conducted at Lotus Labs Pvt. Ltd, Mylapore, Chennai, India between 8th and 19th September 2011. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study 2352/11 was conducted in 36 healthy volunteers and compared Pregabalin, 300 mg, capsules with Lyrica, 300 mg, hard capsules. The study was conducted at Lotus Labs Pvt. Ltd., Vasanthanagar, Bangalore, India between 13th and 29th October 2011. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence studies, pregabalin 50 mg capsules are considered bioequivalent with Lyrica 50 mg capsules and pregabalin 300 mg capsules are considered bioequivalent with Lyrica 300 mg capsules.

The results of study 2353/11 with the 50 mg formulation CAN be extrapolated to the strength 25 mg, and the results of study 2352/11 with the 300 mg formulation CAN be extrapolated to the strengths 75, 100, 150, 200 and 225 mg according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

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

The MAH submitted the version 1.0 RMP dated 1st of July 2014 and proposed the following summary safety concerns:

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
Important potential risks	Suicidality
	Haemangiosarcoma
	Abuse, Misuse, and Drug Dependence
	Off-label use in paedatric patients
Missing information	Use in pregnancy
	Use in lactation

The MAH omitted an important potential risks “medication error with pregabalin oral solution” identified in the originators RMP, which is acceptable since the MAH has not applied for a marketing authorization of oral solution of pregabalin.

The MAH is requested to reword the important missing information”use in pregnancy” and “use in lactation” to “pregnant and lactating women” according to the originators RMP.

There are no special recommendations in place for pregabalin and therefore routine pharmacovigilance activities are considered sufficient at this time. Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

The following risk minimization activities were proposed by the MAH by safety concern:

VI.1.4 Summary table of risk minimisation measures

Important identified risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Weight gain	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Section 4.8 of the SmPC	N/A
Peripheral Oedema and Oedema–related events	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Section 4.8 of the SmPC.	N/A
Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Sections 4.4, 4.7 and 4.8 of the SmPC.	N/A
Discontinuation Events	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Sections 4.4 and 4.8 of the SmPC.	N/A
Drug interactions (lorazepam, ethanol, and CNS depressants)	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Section 4.5 of the SmPC.	N/A
Euphoria	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in Section 4.8 of the SmPC.	N/A
Hypersensitivity and Allergic Reactions	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in sections 4.3, 4.4 and 4.8 of the SmPC.	N/A
Congestive heart failure	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A
Vision-related events	Routine pharmacovigilance activities are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A

Important potential risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Suicidality	1) Routine pharmacovigilance activities are sufficient for this	N/A

	safety concern as information is included in sections 4.4 of the SmPC. 2) Place on monitoring list as part of signal management activities.	
Haemangiosarcoma	1) Routine pharmacovigilance activities are sufficient for this safety concern as information is included in section 5.3 of the SmPC. 2) Place on monitoring list as part of signal management activities	N/A
Abuse, Misuse, and Drug Dependence	1) Abuse information is included in section 4.4 of the SmPC. Misuse and drug dependence are not listed in the SmPC 2) Place on monitoring list as part of signal management activities.	N/A
Off-label use in paediatric patients	1) Information is included in section 4.2 of the SmPC. 2) Place on monitoring list as part of signal management activities.	N/A

Missing information		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Use in Pregnancy	1) Information is included in section 4.6 of the SmPC 2) Place on monitoring list as part of signal management activities	N/A
Use in lactation	1) Information is included in section 4.6 of the SmPC 2) Place on monitoring list as part of signal management activities	N/A

The MAH has satisfactory responded to the questions raised at day 70/day 100 and updated the RMP accordingly. The issues are resolved.

V. 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 PIL 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Brieka, 25, 50, 75, 100, 150, 200, 225 and 300 mg, capsule, hard, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Brieka, 25, 50, 75, 100, 150, 200, 225 and 300 mg, capsule, hard, was positively finalised on 2015-06-11.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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