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Autoridade Nacional do Medicamento
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# Summary Public Assessment Report

# Generics

## Preglenix

75 mg, 150 mg, 300 mg, capsules, hard

**(*Pregabalin)***

## PT/H/1319/001-003/DC

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Pregabalin 75 mg, 150 mg, 300 mg, capsules, hard

This is a summary of the public assessment report (PAR) for Preglenix. It explains how Preglenix was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Preglenix.

For practical information about using Preglenix patients should read the package leaflet or contact their doctor or pharmacist.

## What is Preglenix and what is it used for?

Preglenix 75 mg, 150 mg, 300 mg, capsules, hard is a 'generic medicine'. This means that Preglenix 75 mg, 150 mg, 300 mg, capsules, hard is similar to a 'reference medicine' already authorised in the European Union (EU) called Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, Capsule, hard by Pfizer Limited, registered since 06-07-2004.

Preglenix belongs to a group of medicines used to treat Epilepsy and Generalised Anxiety Disorder (GAD) in adults.

**Epilepsy:** Preglenix is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation) in adults. Your doctor will prescribe Preglenix for you to help treat your epilepsy when your current treatment is not controlling your condition. You should take Preglenix in addition to your current treatment. Preglenix is not intended to be used alone, but must always be used in combination with other anti-epileptic treatment.

**Generalised Anxiety Disorder:** Preglenix is used to treat Generalised Anxiety Disorder (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.

*There are other therapeutic indications approved on day 210 of this DCP which are under patent as per information of the applicant.*

## How does Preglenix work?

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics.
The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

**Mechanism of action**
Pregabalin binds to an auxiliary subunit ($\alpha_2$-δ protein) of voltage-gated calcium channels in the central nervous system.

## How is Preglenix used?

The pharmaceutical form of Preglenix is capsules, hard and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

## What benefits of Preglenix have been shown in studies?

Because Preglenix is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Lyrica. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
The company provided data from the published literature on Pregabalin.

## What are the possible side effects of Preglenix?

Because Preglenix is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

## Why is Preglenix approved?

It was concluded that, in accordance with EU requirements, Preglenix has been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the INFARMED; I.P. decided that, as for reference medicine called Lyrica, the benefits are greater than its risk and recommended that it can be approved for use.

## What measures are being taken to ensure the safe and effective use of Preglenix?

A risk management plan - Version 1, dated 15-07-2014 - has been developed to ensure that Preglenix is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Preglenix including the appropriate precautions to be followed by healthcare professionals and patients.

**Summary of Safety Concerns:**

**Table 1.** Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | 1. Weight gain<br>2. Oedema<br>3. Dizziness, somnolence and the potential for accidental injury<br>4. Withdrawal effects<br>5. Drug interactions (including lorazepam, ethanol and CNS depressants)<br>6. Euphoria<br>7. Hypersensitivity<br>8. Congestive cardiac failure<br>9. Vision related effects |
| Important potential risks | 1. Haemangiosarcoma<br>2. Suicidal ideation and behaviour<br>3. Off-label use in paediatric patients<br>4. Abuse, misuse and drug dependence |
| Missing information | 1. Drug exposure during pregnancy and lactation |

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored continuously as well.

## Other information about Preglenix

The marketing authorisation for Preglenix was granted on 06-11-2015.

The full PAR for Preglenix 75 mg, 150 mg, 300 mg, capsules, hard can be found on the website http://www.infarmed.pt/infomed/inicio.php. For more information about treatment with Preglenix 75 mg, 150 mg, 300 mg, capsules, hard, read the package leaflet or contact your doctor or pharmacist.

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# Public Assessment Report

# Scientific discussion

## Preglenix

75 mg, 150 mg, 300 mg, capsules, hard

**(*Pregabalin)***

## PT/H/1319/001-003/DC

**This module reflects the scientific discussion for the approval of Preglenix. The procedure was finalised at 23-06-2015. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed in granting a marketing authorisation for Preglenix 75 mg, 150 mg, 300 mg, capsules, hard, from Glenmark Pharmaceuticals s.r.o.

Preglenix 75 mg, 150 mg and 300 mg, capsules, hard is indicated for:

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

***Generalised Anxiety Disorder***
Preglenix is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

The safety and efficacy of the reference product in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.

*There are other therapeutic indications approved on day 210 of this DCP which are under patent as per information of the applicant.*

**Posology**
The dose range is 150 to 600 mg per day given in either two or three divided doses.

***Epilepsy***
Pregabalin treatment can be started with a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.

***Generalised Anxiety Disorder***
The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

***Discontinuation of pregabalin***
In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

With Portugal as the Reference Member State in this Decentralized Procedure, Glenmark Pharmaceuticals s.r.o. is applying for the Marketing Authorisations for Preglenix 75 mg, 150 mg, 300 mg, capsules, hard in CZ, PL, RO, SK (CMS).

The marketing authorization was granted on 06-11-2015 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph (generic medicinal product) and the Marketing Authorisation Holder is Glenmark Pharmaceuticals s.r.o.

The originator product is Lyrica, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, capsule, hard (strengths, pharmaceutical form) by Pf75 mg, 150 mg, 300 mg, capsules, hard izer Limited, registered since 6th July 2004.

This generic application is applying for all indications of the reference product.

# II. QUALITY ASPECTS

## II.1 Introduction

The pharmaceutical form is capsule, hard

**75 mg:** Red opaque cap/ White opaque body, size "4" hard gelatin capsules imprinted with 'PG' on cap and '75' on body with black ink.

**150 mg:** White opaque cap/ White opaque body, size "2" hard gelatin capsules imprinted with 'PG' on cap and '150' on body with black ink.

**300 mg:** Red opaque cap/ White opaque body, size "0" hard gelatin capsules imprinted with 'PG' on cap and '300' on body with black ink.

The excipients are: starch pregelatinised, talc (E553b), gelatin, titanium dioxide (E171), sodium laurilsulphate, black ink (which contains shellac, propylene glycol, iron oxide black (E172), and potassium hydroxide) and water.
**The 75 mg and 300 mg capsules** also contain iron oxide red (E172).

Preglenix are supplied in PVC/Aluminium blister in pack sizes of 14, 21, 56, 60 or 84 hard capsules.

Preglenix are also supplied in white opaque HDPE bottle with white opaque polypropylene child resistant cap containing 30, 200, or 500 hard capsules.

Not all pack sizes may be marketed.

## II.2 Drug Substance

Pregabalin is not described in the Ph.Eur.

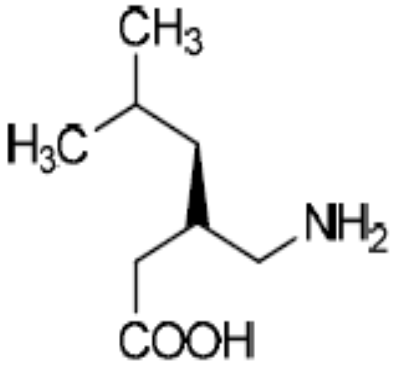
## *II.3 General Information:*

**Nomenclature**

Generic name: Pregabalin

Chemical names: (S)-(+)-3-(amino methyl)-5-methylhexanoic acid

Structure (structural formula)




Molecular formula: $C_8H_{17}NO_2$

Relative molecular mass: 159.23 g/mol

Polymorphism:The manufacturer commercially produces (S)-3-(aminomethyl)-5-methylhexanoic acid (Form-I).

Isomerism: Pregabalin (or) (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid contains one chiral centre, but is synthesised as the "S enantiomer".

**General properties (physico-chemical characterisation)**

Description: white to off-white crystalline powder
Solubility: Sparingly soluble in water and practically insoluble in acetone.

Solubility profile:

Water: 23.6 mg/ml at 25ºC

Buffer solutions:

| Solvent | Quantity Dissolved (mg/mL) at 25°C |
|---|---|
| Buffer having pH 1.2 | 50.5 |
| Buffer having pH 4.0 | 33.3 |
| Buffer having pH 7.0 | 31.2 |

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to pregabalin are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 24 months is justified.

### II.4 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 24 months without any special storage conditions for the drug product packed in PVC – Aluminum blisters packs or HDPE bottles is considered acceptable.

## III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Preglenix 75 mg, 150 mg, 300 mg, capsules, hard 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.

## IV. CLINICAL ASPECTS

To support the application, the applicant has submitted, as report, two bioequivalence studies, namely, 170-12 a pivotal bioequivalence study in 24 healthy subjects for the 300 mg strength and Study 169-12 , a pivotal bioequivalence study in 24 healthy subjects for the 50 mg strength.

**Biowaiver**

According to the EMA guideline on the investigation of bioequivalence; following general requirements must be met where a waiver for additional strength(s) is claimed:

- All the strengths i.e. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg of proposed pharmaceutical products are manufactured by using the same manufacturing process,

- The qualitative composition of the pregabalin capsules 25mg, 75mg, 100mg, 150mg, 200 mg and 225 mg is same as that of pregabalin capsules 50mg and 300mg.

- The composition of strengths i.e. 25mg and 50mg are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is same.
- Similarly, the composition of strengths i.e. 75mg, 100mg, 150mg, 200mg, 225mg and 300mg are quantitatively proportional w.r.t amount of each excipient to the amount of active substance(s) refer table below for quantitative composition.

- The in-vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 25mg and the strength of batch used in the bioequivalence studies i.e. 50 mg.

- Similarly, in-vitro dissolution profile of 75mg, 100mg, 150mg, 200mg and 225mg strengths are found similar under identical conditions to the batch used in the bioequivalence studies i.e. 300mg.

- Pregabalin exhibit linear pharmacokinetics in dose range of 25-300mg.

**Conclusion on bioequivalence studies:**

Based on the submitted bioequivalence studies Preglenix 75 mg, 150 mg, 300 mg, capsules, hard is considered bioequivalent with Lyrica, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, capsule, hard.

## IV.1 Risk Management Plan

The MAH has submitted a risk management plan - Version 1, dated 03-02-2015 -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 Preglenix 75 mg, 150 mg, 300 mg, capsules, hard

**Summary of Safety Concerns:**

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## Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

# V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study (Final Report 16 February 2015) 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 readability user testing of the PIL for **pregabalin 75 mg, 150 mg and 300 mg capsules, hard** was conducted between January 20th, 2015 and February 16th, 2015.

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 application for Preglenix 75 mg, 150 mg and 300 mg, capsules, hard contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.