

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Glepark 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, tablets
Glenmark Generics [Europe] Ltd, United Kingdom

pramipexole dihydrochloride monohydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1319/001-004/DC
Registration number in the Netherlands: RVG 101915, 101918-101920

2 June 2010

Pharmacotherapeutic group:	dopamine agonists
ATC code:	N04BC05
Route of administration:	oral
Therapeutic indication:	signs and symptoms of idiopathic Parkinson's disease with or without levodopa; symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome
Prescription status:	prescription only
Date of authorisation in NL:	26 April 2010
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LT, RO, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Glepark 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg (respectively 0.125, 0.25, 0.5 and 1.0 mg of salt), tablets from Glenmark Generics [Europe] Ltd. The date of authorisation was on 26 April 2010 in the Netherlands.

A comprehensive description of the indications and posology is given in the SPC.

The product is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations) in dosages up to 3.3 mg of base (4.5 mg of salt) per day.

Pramipexole is indicated for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 0.54 mg of base (0.75 mg of salt).

A comprehensive description of the indications and posology is given in the SPC.

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which it has a preferential affinity to D3 receptors, and has full intrinsic activity. Pramipexole alleviates Parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover. The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Sifrol 0.088, 0.18, 0.35, and 0.7 mg tablets, which have been registered via centralised procedure EMEA/H/C/133 by Boehringer Ingelheim International GmbH since 1997.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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' authorised 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. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Sifrol 0.35 mg, from the German market. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is pramipexole dihydrochloride monohydrate, an established active substance, however not described in the European pharmacopoeia (Ph.Eur.*). The active substance is a white to off-white powder, and is soluble in methanol and water. It has two isomers, but the active substance is the S-isomer. The level of the (R)-enantiomer is limited in the active substance specifications. The molecule does not exhibit polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of three steps. No class 1 solvents and/or catalyst are used. The active substance has been adequately characterized. Acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 commercial-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot-scale batches and three production batches stored for up to 24 months at 25°C/60%RH and 6 months at 40°C/75%RH. The batches were adequately stored. The active substance remains stable under accelerated and long term storage conditions for all parameters tested. No specific trends were observed. The proposed retest period of 2 years, without specific storage conditions could therefore be granted.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Glepark 0.088 mg contains as active substance 0.125 mg of pramipexole dihydrochloride monohydrate, corresponding to 0.088 mg of pramipexole base, and is a circular, white, flat bevelled tablets engraved with 'PX' on one side and plain on the other side.

Glepark 0.18 mg contains as active substance 0.25 mg of pramipexole dihydrochloride monohydrate, corresponding to 0.18 mg of pramipexole base, and is an oval, white, flat bevelled uncoated tablets

engraved with 'PX' and '1' on either side of score line on one side and score line on the other side. The tablet can be divided into equal halves.

Glepark 0.35 mg contains as active substance 0.5 mg of pramipexole dihydrochloride monohydrate, corresponding to 0.35 mg of pramipexole base, and is an oval white, flat bevelled uncoated tablets engraved with 'PX' and '2' on either side of score line on one side and score line on other side. The tablet can be divided into equal halves.

Glepark 0.7 mg contains as active substance 1 mg of pramipexole dihydrochloride monohydrate, corresponding to 0.7 mg of pramipexole base, and is an oval, white, flat bevelled uncoated tablets engraved with 'PX' and '3' on either side of score line on one side and score line on other side. The tablet can be divided into equal halves.

The tablets are packed in Aluminium/Aluminium blisters.

The excipients are: mannitol (E421), maize starch, povidone K30 (E1201), colloidal anhydrous silica, magnesium stearate (E470b).

The formulation for 0.088 mg and 0.18 mg tablets is dose weight proportional, while the other strengths have the same weight as that of the 0.18 mg strength, they differ in the amount of active substance and mannitol.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The differences between the formulation of the batches used in the development studies and the final batches is described and justified, and the physicochemical and biological properties are relevant for the performance of the drug product are addressed. Comparative dissolution profiles were determined for all strengths with the innovator product. The 0.18, 0.35, 0.7 mg tablets possess a break line on one side of the tablets. Breakability and content uniformity for these strengths have been demonstrated.

Manufacturing process

The drug product is manufactured by means of wet granulation. The manufacturing process has been adequately described and validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for 3 full-scale batches of all strengths.

Control of excipients

The excipients comply with their Ph.Eur. specifications. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, dissolution, disintegration, water, hardness, friability, uniformity of dosage units, average weight, and microbiological quality. The release and shelf-life requirements are identical, with the exception of the requirements for related substances/degradation products. The proposed limits are considered to be acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 5 commercial-scale batches of the two lower strengths and 3 batches of the two higher strengths. The batches were stored at 25°C/60%RH for 18 months and at 40/75%RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended packaging material (Al-Al blister).

The 18 months stability data at long term and 6 months at accelerated conditions for product packaged in Alu/Alu blisters and 12 months in triple laminated bags show that there is no significant change in the

physical and chemical characteristics of the product from the initial values. All test results remain within the specifications, no trends for assay have been observed yet. Based on the submitted data, a shelf life of 24 months, when stored in the original package, was granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A statement was provided that none of the excipients are of human origin. TSE/BSE certificates from suppliers for each of the excipients have been included.

II.2 Non clinical aspects

These products are generic formulations of Sifrol 0.088, 0.18, 0.35, and 0.7 mg tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pramipexole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Pramipexole is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Glepark 0.35 mg (Glenmark Generics Ltd, UK) is compared with the pharmacokinetic profile of the reference product Sifrol 0.35 mg tablets (Boehringer Ingelheim) registered in the EU by a centralised procedure and obtained from the German market.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, open-label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-43 years. Each subject received a single dose (0.35 mg) of one of the 2 pramipexole formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Three subjects were withdrawn from the study: one tested positive for morphine, two subjects were withdrawn due to adverse events after dosing in period 2. One subject experienced emesis in period 1, and was also excluded from pharmacokinetic and statistical analysis. Data of 32 subjects were included in the analyses.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} (median, range)) of pramipexole under fasted conditions.

Treatment N=32	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	11.2 \pm 1.6	11.6 \pm 1.6	0.93 \pm 0.14	2.25 (0.5-6.0)	7.4 \pm 1.1
Reference	11.2 \pm 1.9	11.6 \pm 1.9	0.89 \pm 0.17	3.0 (0.75-6.0)	7.3 \pm 0.9
*Ratio (90% CI)	1.00 (0.96-1.05)	1.00 (0.96-1.04)	1.06 (1.00-1.11)	-	-
CV (%)	10.0	9.8	12.2	-	-
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of pramipexole under fasted conditions, it can be concluded that Glepark 0.35 mg and Sifrol 0.35 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Pramipexole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of pramipexole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths

Pharmacokinetics of pramipexole are dose linear, and the pharmaceutical products are manufactured by the same process and manufacturer. The 0.18 mg and 0.7 mg tablets have the same composition and total weight as the 0.35 mg tablets with the exception of the active substance (less than 5% of the total weight). The 0.088 mg tablets are dose proportional with the 0.18 mg tablets. In addition, the dissolution profile is similar under identical conditions for the additional strengths and the strength of the biobatch. Therefore, the results of the bioequivalence study performed with the 0.35 mg tablets apply to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Pramipexole was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pramipexole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. Nineteen questions were asked: 16 questions specific to pramipexole (addressing key issues) and 3 questions on user friendliness of the PIL. In both rounds, scoring on each and every question met the criterion of 81% correct answers. Based on the test results, no revisions to the PIL were deemed necessary.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Glepark 0.088 mg, 0.18 mg, 0.35 mg and 0.7 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Sifrol 0.088, 0.18, 0.35, and 0.7 mg tablets. Sifrol tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other pramipexole containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Glepark 0.088 mg, 0.18 mg, 0.35 mg and 0.7 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 8 February 2009. Glepark 0.088 mg, 0.18 mg, 0.35 mg and 0.7 mg, tablets were authorised in the Netherlands on 26 April 2010.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from February 2009 to 14 April 2009, to coincide with the data lock point of the innovator.

The date for the first renewal will be: 8 February 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to place commercial-scale batches on stability and to report any out of specification results to the authorities.

Risk management

- The MAH committed to follow the RMP and SPC of the innovator product and the risk minimisation activities of the innovator in the future, where appropriate.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Name change of MAH in BG, CZ, HU, RO, SK.	NL/H/1319/001-004/IA/002	IA	4-1-2010	18-1-2010	Approval	N
Change of manufacturer responsible for batch release and control testing.	NL/H/1319/001-004/IA/003	IA	4-1-2010	18-1-2010	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.	NL/H/1319/002+004/IA/004	IA	4-1-2010	14-4-2010	Approval	N
Replacement or addition of a manufacturer responsible for batch release including batch control/ testing.	NL/H/1319/002+004/IA/005	IA	15-3-2010	14-4-2010	Approval	N