CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ropinirol Aurobindo 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg, film-coated tablets Aurobindo Pharma B.V., the Netherlands

ropinirole hydrochloride

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 106922, 106925 – 106927, 106929

28 October 2014

Pharmacotherapeutic group:	dopamine agonists
ATC code:	N04BC04
Route of administration:	oral
Therapeutic indication:	treatment of Parkinson's disease; symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	25 April 2012
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 (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Ropinirol Aurobindo 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg, film-coated tablets, from Aurobindo Pharma B.V. The date of authorisation was on 25 April 2012 in the Netherlands.

The product is indicated for:

- treatment of Parkinson's disease under the following conditions: Initial treatment as monotherapy in order to delay the introduction of levodopa. In combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations.
- *Only 0.25 mg, 0.5 mg, 1 mg, 2 mg strength* - symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

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

Ropinirole is a non ergoline dopamine agonist.

Parkinson's disease
Ropinirole alleviates the dopamine deficiency which characterises Parkinson's disease by stimulating striatal dopamine receptors. Additionally, ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

Restless Legs Syndrome
A 12-week placebo-controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements during sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12.

This national procedure concerns a generic application claiming essential similarity with the innovator product Requip 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 5 mg tablets (NL license RVG 20761-5) which has been registered in the Netherlands by GlaxoSmithKline B.V. since 1996 (original product). Requip is part of mutual recognition procedure FR/H/111/001-005.

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 Requip 1 mg tablets, registered in the United Kingdom. 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. This generic product can be used instead of its 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, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 this product type 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 ropinirole hydrochloride, an established active substance which is however not described in any pharmacopoeia. The active substance is freely soluble in water and soluble in methanol. Only one crystalline form of ropinirole HCl exists.

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 5 steps. Ropinirole hydrochloride has adequately been characterized. All specifications for solvents, starting materials and reagents are acceptable.

Quality control of drug substance
In the specification the limits for residual solvents have been adequately substantiated. It has been demonstrated that all class 2 residual solvents remain clearly below the ICH limits and therefore have not been included in the specification. The specification is considered to be acceptable and batch analytical data demonstrating compliance with the drug substance specification have been provided from three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scaled and 3 pilot scaled batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). During the long term and accelerated studies only a decrease in residual solvents is observed. No other trends were observed. The proposed retest period of 4 years without special storage conditions can be granted.

Medicinal Product

Composition
Ropinirol Aurobindo 0.25 mg are white to off-white, circular, biconvex, film-coated tablets debossed with 'F' on one side and '61' on the other side.
Ropinirol Aurobindo 0.5 mg are yellow, circular, biconvex, film-coated tablets debossed with 'F' on one side and '62' on the other side.
Ropinirol Aurobindo 1 mg are green, circular, biconvex, film-coated tablets debossed with 'F' on one side and '63' on the other side.
Ropinirol Aurobindo 2 mg are pink, circular, biconvex, film-coated tablets debossed with 'F' on one side and '64' on the other side.
Ropinirol Aurobindo 5 mg are blue, circular, biconvex, film-coated tablets debossed with 'F' on one side and '70' on the other side.

The tablets are packed in polyamide/aluminium/PVC – aluminium blister packs and white HDPE bottles with polypropylene cap en a desiccant sac with silicagel.

The excipients are:
Tablet core: lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate.
Film-coating: hypromellose, titanium dioxide (E171), macrogol, and;
0.25 mg: polysorbate 80
0.5 mg: iron oxide yellow (E172), iron oxide red (E172)
1 mg: iron oxide yellow (E172), indigotine (E132)
2 mg: iron oxide yellow (E172), iron oxide red (E172)
5 mg: polysorbate 80, indigotine (E132).

The different tablet strengths have the same composition, except for the amount of active substance and lactose as filler.

Pharmaceutical development
The pharmaceutical development has been adequately described. The excipients and the container closure system are deemed acceptable as they are usual for this type of dosage form. A look-a-like approach is applied for the different strength, i.e. tablet weight is kept constant. The 1 mg proposed drug product has been compared to the 1 mg strength of the innovator and to one batch of the 0.25 mg, 0.5 mg, 2 mg and 5 mg strengths, demonstrating more than 85% is dissolved after 5 minutes in all cases. Therefore the dissolution profiles are considered essentially similar. The 1 mg strength has been used in the bioequivalence study and the biowaiver for the other strengths is deemed acceptable from a chemical-pharmaceutical point of view.

Manufacturing process
The product is manufactured through a wet granulation process. This process consists of dry mixing, granulation, drying, sifting, milling, lubrication, compression into tablets and coating. The manufacturing process has been adequately validated according to relevant European guidelines. The process is considered non-standard because of the low active substance content. Process validation data on the product has been presented for three pilot-scale batches of each strength.

Control of excipients
The excipients comply with Ph.Eur. requirements and in-house tests. Additional non-mandatory functionality tests as described in the Ph.Eur. monographs of the excipients are included, where necessary. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, water, dissolution, uniformity of dosage units, assay, related substances, thickness, identification of colourants and microbial limits. Release and shelf-life specifications are identical except for water, assay and related substances. Separate limits for related substances arte applied after opening of the HDPE container due to the observed increase in one impurity from the in-use stability study.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on 3 pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on 15 pilot-scale batches stored at 25°C/60%RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (3 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in triple laminated blisters and HDPE containers. The 5 mg strength is packed in HDPE containers only.
For the tablets packed in blisters and HDPE the stability results show that the samples incubated at accelerated conditions showed a significant increase in the levels of related substances after 3 months. After 12 months intermediate and 24 months long-term study, variability in assay and water content and an increase in impurities were observed, with a significant change in assay for one batch at intermediate conditions. This is covered by the lower assay shelf-life limit. Photostability of the drug product has been

demonstrated. The proposed shelf-life of two years if stored below 30°C in the original package in order to protect from moisture can be granted.

In-use stability testing has been done for the 0.25 mg and 5 mg tablets packed in HDPE containers, simulating sample withdrawal, for 6 months at 25°C/60%RH. A slight increase in water and impurities and a decrease in assay were observed. The MAH repeated the in-use stability with 24 month old samples with improved simulation of daily practice. Results demonstrated an increase in impurities, but results remained within limits. The proposed shelf-life after opening of three months is therefore acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose monohydrate, a declaration has been provided that lactose is manufactured using milk sourced from healthy animals in the same conditions as milk collected for human consumption and using no other ruminant material except calf rennet are unlikely to present risk of TSE contamination as per the note for guidance on minimizing risk of transmissible animal spongiform encephalopathy via human & veterinary products (EMEA/410/01 Rev-02). Magnesium stearate is of vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Requip, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

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 ropinirole 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

Ropinirole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ropinirol Aurobindo 1 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Requib 1 mg tablets (GlaxoSmithKline, UK).

The choice of the reference product
The choice of the reference product from the UK for the bioequivalence study is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The 1 mg dose was chosen in view of the high incidence of adverse events when the drug is administered to healthy subjects.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 19-46 years. Each subject received a single dose (1 mg) of one of the 2 ropinirole formulations. The tablet was orally administered 30 minutes after having a standardized non high-fat meal and prior fasting of 10 hours.
There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 30.00 and 36.00 hours after administration of the products.

The study design is acceptable. According to the innovator SmPC, tablets need to be taken with a meal to improve gastric tolerability. The current guideline requires a high-fat meal, for reasons of standardisation. As this application was submitted under the previous guideline (CPMP/QWP/EWP/1401/98), the low-fat meal is considered acceptable. Moreover, according to literature data no significant pharmacokinetic interaction effect of food is expected requiring a high-fat meal.

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 during the first period due to vomiting and two subjects did not check in for the second period of the study. Thirty-one subjects completed the study and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ropinirole under fed conditions.

Treatment N=31	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14.33 ± 6.12	14.72 ± 6.28	1.64 ± 0.45	3.00 (0.33 – 5.00)	4.6 ± 1.3
Reference	16.19 ± 6.82	16.58 ± 7.02	1.80 ± 0.49	3.00 (0.67 – 6.00)	5.3 ± 1.8
***Ratio (90% CI)**	0.89 (0.83 – 0.97)	0.90 (0.83 – 0.97)	0.92 (0.87 – 0.97)	--	--
CV (%)	19.0	18.9	13.7	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 ropinirole under fasted conditions, it can be concluded that Ropinirol Aurobindo 1 mg and Requib 1 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.

Biowaiver
The different tablet strengths have the same composition, except for the amount of active substance and lactose as filler to compensate the differences in active substance. The amount of active substance is less than 5% in all tablets. The tablets are manufactured by the same manufacturer and the same manufacturing process. The dissolution test at different pH values shows comparable dissolution (>80% dissolved within 15 min.). In addition, ropinirole shows linear pharmacokinetics. Therefore, the results obtained for the 1 mg strength can be extrapolated to the 0.25, 0.5, 2 and 5 mg tablets.

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

Ropinirole was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ropinirole 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 SmPC. 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

SmPC

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Requip.

Readability test

The package leaflet has not been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Reference was made to the PL for another ropinirole product, which has been user tested. As the PL for Ropinirol Aurobindo is in accordance with this package leaflet, no separate user test is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ropinirol Aurobindo 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Requip 0.25/0.5/1/2/5 mg film-coated tablets. Requip 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 SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other ropinirole containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Ropinirol Aurobindo 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg, film-coated tablets were authorised in the Netherlands on 25 April 2012.

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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	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	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation.	MA Transfer	13-7-2012	13-9-2012	Approval	N
Change to the product information following the PhVWP/CMDh decision on levodopa, dopamine agonists and COMT inhibitors – Risk of impulse control disorders.	IB	3-10-2012	2-12-2012	Approval	N
Introduction of the PSMF to replace the Detailed Description of Pharmacovigilance System in accordance with new pharmaco-vigilance legislation.	IA/G	27-5-2013	12-6-2013	Approval	N