Decentralised Procedure

Public Assessment Report

Ropinirol dura 0,25 mg, 0,5 mg, 1 mg, 2 mg, 5 mg
Ropinirol Merck 0,25 mg, 0,5 mg, 1 mg, 2 mg, 5 mg
Ropinirol hydrochloride

DE/H/0957/001- 005/DC
DE/H/0981/001- 005/DC

Applicant: Generics [UK]Limited

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Ropinirol dura Ropinirol Merck
INN (or common name) of the active substance(s):	Ropinirol hydrochloride
Pharmaco-therapeutic group (ATC Code):	N04BC04
Pharmaceutical form(s) and strength(s):	Film-coated Tablets 0,25 mg, 0,5 mg 1 mg, 2 mg, 5 mg
Reference Number for the Decentralised Procedure	DE/H/0957/01-05/DC Ropinirol dura DE/H/0981/01-05/DC Ropinirol Merck
Reference Member State:	Germany
Member States concerned:	DE/H/0957/01-05/DC Ropinirol dura: AT, BE, CZ, DK, EL, ES, FI, FR, HU, IE, IT, NL, NO, PT, SE, SI, SK, UK DE/H/0981/01-05/DC Ropinirol Merck : FR
Applicant (name and address)	Generics [UK] Limited Alabny Gate, Darkes Lane, Potters Bar, Hertfordshire, EN6 1AG, United Kingdom
Names and addresses of manufacturers of dosage form	Torrent Pharmaceuticals Limited, Address: Ahmedabad-Mehsana Highway, P.O. Indrad Taluka Kadi, Dist. Mehsana-382721,Gujarat, India
Names and addresses of manufacturers responsible for batch release in the EEA	McDermott Laboratories t/a Gerard Laboratories Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland Merck Farma y quimica Poligono Merck, E-08100, Mollet del Valles, Barcelona Spain AUSTRIA ONLY: Merck KgaA & Co. Werk Spittal Hösslgasse 20. 9800 Spittal/Drau Austria FRANCE ONLY: Merck Generiques ZAC des Gaulnes, 10 boulevard de Lattre de Tassigny, 69330 Meyzieu France FRANCE ONLY: Merck Generiques 34 rue Saint Romain, 69359 Lyon Cedex 08 France THE NETHERLANDS ONLY: Name of Company: Merck Generics Address: Dieselweg 26, 3752 LB Bunschoten Country: The Netherlands

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS and CMS have approved the application for Ropinirol dura, in the treatment of Parkinson's disease and Restless Legs Sydrome (RLS).

II. EXECUTIVE SUMMARY

II.1 Problem statement

These are decentralised applications with Germany as the reference member state (RMS) submitted in accordance with article 10(1) of Directive 2001/83/EC as amended for Ropinirol dura 0.25 mg, 0.5 mg, 1 mg, 2 mg, 5 mg tablets claiming essential similarity to Requip tablets marked in Germany by GlaxoSmithKline.

The first authorisation for Requip 0,25 mg film coated tablets was granted on 2nd July 1996 in the United Kingdom. Consequently, data protection period is already expired and reference can be made to the documentation of the originator.

II.2 About the product

Ropinirole is a non-ergoline dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes.

The precise mode of action of ropinirole as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of postsynaptic dopamine D_2 -type receptors within the caudate-putamen in the brain. This conclusion is supported by studies that show that ropinirole improves motor function in various animal models of Parkinson's disease.

Furthermore ropinirole is indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS). But this application does not include this indication.

II.3 General comments on the submitted dossier

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to ropinirole hydrochloride 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, showing the molecule to be very stable. The proposed retest period of 24 months is justified.

Drug Product

The product is straight forward formulated instant release tablet, manufactured with standard procedures.

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 of each strength. 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 with no further storage recommendations for the drug product is considered acceptable.

III.2 Nonclinical aspects

Pharmacology
Dopamine (3,4-dihydroxyphenylethylamine, DA) is a major neurotransmitter in the central nervous system (CNS), especially in the basal ganglia, and is i. a. involved in movement control. Degeneration of dopaminergic innervation in the substantia nigra pars compacta is the reason for the movement impairments seen in idiopathic Parkinsons disease, and stimulation of DA receptors ameliorates these symptoms. Therapeutically dopamine receptors are activated by dopamine itself derived from the metabolic precursor of DA, levodopa (L-3,4-dihydroxyphenylalanine), which passes the blood-brain-barrier and is then transformed to dopamine, or by direct dopamine receptor agonists. Ropinirole is a non-ergoline dopamine full agonist. It binds with high affinity to dopamine D_2- and D_3-receptors with a higher affinity to the latter. The relevance of the activation of dopamine D_3-receptors in Parkinsons disease is not yet elucidated but activation of D_2-receptors appears to be crucial for benefit. Besides moderate binding to opioid receptors, ropinirole lacks affinity to D_1-, 5-HT_1-, 5-HT_2-, benzodiazepine-, muscarine- and - and -adrenergic receptors. Ropinirole showed in vivo dopaminergic acticity in several animal models including MPTP-induced Parkinsons syndrome in primates.

Pharmacokinetics
Following oral administration, ropinirole is almost completely absorbed. Peak blood levels are

observed after about 1 to 2 hours. Due to first pass elimination, bioavailability is only about 50 %. Bioavailability increases with dose. The volume of distribution is more than unity and amounts to 6.7 L/kg in humans. Plasma protein binding is 10 to 40 %. Metabolisation is mainly due to CYP1A2, and metabolites have only marginal dopaminergic activity. Ropinirole is mainly excreted via urine, and terminal half-life is about 6 hours. Only 10 % of the dose is recovered as unchanged substance in the urine.

Toxicology
The toxicological profile of ropinirole is mainly due to its pharmacological effect (behavioural changes, hyperprolactinaemia, decrease of blood pressure and heart rate, ptosis and salivation). In a battery of in vitro and in vivo tests no relevant signs of genotoxicity were observed. In a 2 years carcinogenicity study in mice no carcinogenic effects were observed. In a 2 years study in rats hyperplasia of Leydig cells and adenomas of the testis were found, probably as a consequence of the hyperprolactinaemia produced by ropinirole. Therefore these lesions appear to be species-specific.In a rat reproduction study ropinirole reduced fetal weight, increased postimplatation loss and induced malformation of toes. In rabbits there were no signs for developmental impairment.

III.3 Clinical aspects

About ropinirole in the therapy of Parkinson's disease and RLS.

Ropinirole is in use for treatment of idiopathic Parkinson's disease and RLS.
Parkinson's disease results from a selective loss of dopaminergic neurons in the pars compacta of the substantia nigra, a midbrain structure with projections to the striatum. Parkinson's disease affects about 1-2% of individuals over the age of 65 years. The cardinal signs of Parkinson's disease include tremor, rigidity, akinesia or bradykinesia and postural instability. These symptoms of Parkinson's disease do not develop until approximately 70-80% of the nigral dopaminergic neurons have degenerated.
So far medical strategies have focused mainly on either dopamine replacement or otherwise enhancing the dopaminergic response. Current research on anti-parkinsonian drugs focuses on palliative therapy and several drugs are presently in use for the symptomatic therapy of Parkinson's disease.

Levodopa is the most effective drug in the treatment of Parkinson disease. It improves significantly the symptoms of Parkinson disease, but it cannot stop the progression of the disease.

The other drugs used in the treatment of Parkinson disease are synthetic dopamine receptor agonists, amantadine and monoamine oxidase B inhibitors like seligiline. The dopamine agonists being ergot derivatives like are bromocriptine, pergolide, lisuride and carbagoline and non-ergot derivatives like are pramipexole, ropinirole, piribedil and apomorphine.

Patients with Parkinson disease on long term levodopa treatment have close to 80% frequency of dyskinesias. To minimize end-of-dose effects encountered with levodopa therapy, dopamine agonists with relative long half-lives were introduced in the US, beginning with bromocriptine in 1976 and pergolide in 1988. Both agonists have been used primarily as adjuncts to levodopa. Ropinirole is used without levodopa and as an adjuvant to levodopa therapy. In the early stages of the disease ropinirole is as effective as levodopa, in the later stages the effectivness of ropinirole is less than levodopa. Concomitant use of ropinirole with levodopa reduces the off-phases.

Furthermore ropinirole is used for treatment of RLS and efficacy was demonstrated in several studies. RLS, a sleep-related disorder with an estimated prevalence of 1 % to 5 % is characterized by unpleasant sensations experienced predominantly in the legs, which occur only at rest and become more pronounced in the evening or at night. The onset of this disorder is usually after 30 years of age and the prevalence increases with age. The etiology of RLS is unknown. It is hypothesized that periodic limb movements during sleep (a similar disease) results from a disinhibition of descending inhibitory pathways. Disturbances in dopaminergic, adrenergic and opiate systems may contribute to RLS.

Pharmacodynamics

The pharmacokinetics of ropinirole is similar in Parkinson's disease patients and patients with Restless Legs Syndrome. Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1-2 hours. In clinical studies, over 88% of a radiolabeled dose was recovered in urine and the absolute bioavailability was 55%, indicating a first-pass effect. Relative bioavailability from a tablet compared to an oral solution is 85%. Food does not affect the extent of absorption of ropinirole, although its T_{max} is increased by 2.5 hours and its C_{max} is decreased by approximately 25% when the drug is taken with a high-fat meal. The clearance of ropinirole after oral administration to patients is 47 L/hr (cv = 45%) and its elimination half-life is approximately 6 hours. Ropinirole is extensively metabolized by the liver to inactive metabolites. Steady-state concentrations are expected to be achieved within 2 days of dosing. Accumulation upon multiple dosing is predictive from single dosing.

Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg (cv = 32%). It is up to 40% bound to plasma proteins

Clinical efficacy and Clinical safety:

No specific clinical studies in patients were required for the applications submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended. An appropriate literature review has been conducted which supports the use of ropinirole in the proposed indications that are identical to those approved for the reference product Requip. Safety issues have also been appropriately addressed in the clinical overview.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data and bioequivalence has been shown for Ropinirol dura 1 mg film-coated tablets.
In the day 160 ARD the applicant decided to additionally include the indication RLS as proposed by the CMS the Netherlands. We agree with the additional inclusion of the indication RLS for the strengths 0,25 mg, 0,5 mg, 1 mg and 2 mg but not for the 5 mg strength.
Based on the review of the data and the Applicant’s response to the questions raised by RMS and CMS on quality, safety and efficacy, the RMS and CMS have approved the application for Ropinirole dura for the strengths 0,25 mg, 0,5 mg, 1 mg and 2 mg in the treatment of Parkinson’ s disease and RLS, furthermore the RMS and CMS have approved the application for Ropinirole dura for the strength 5 mg for the only indication Parkinson’ s disease.