IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1077/107/003
Case No: 2030387

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

GlaxoSmithKline (Ireland) Ltd

Stonemasons Way, **Rathfarnham**, **Dublin 16**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Vunexin 1mg film coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/08/2007** until **30/11/2011**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vunexin 1mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of ropinirole (as hydrochloride).

Excipient(s):
Lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Green oval-shaped, marked "GS" on one side and "SJG" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

VUNEXIN is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1).

4.2 Posology and method of administration

Oral use.

Adults

Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken just before bedtime, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

Treatment initiation (week 1)

The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards)

Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.

The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in table 1.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 1 Dose titration

Week	2	3	4	5*	6*	7*
Dose (mg)/once daily	1	1.5	2	2.5	3	4

* To achieve optimal improvement in some patients.

The patient's response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Children and adolescents

VUNEXIN is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Elderly

The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

Renal impairment

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Severe renal impairment (creatinine clearance <30ml/min)
Severe hepatic impairment.

4.4 Special warnings and precautions for use

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Patients with major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson's disease. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factord such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP 1A2. A pharmacokinetic study (with a ropinirole dose of 2mg, three times a day) revealed that ciprofloxacin increased the Cmax and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP 1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a dose of 2mg, three times a day) and theophylline, a substrate of CYP 1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.
Based on *in-vitro* data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with ropinirole, dose adjustment maybe required.

Increased plasma concentrations of ropinirole have been observed in patients treated with hormone replacement therapy. In patients already receiving hormone replacement therapy, ropinirole treatment may be initiated in the usual manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if hormone replacement therapy is stopped or introduced during treatment with ropinirole.

No pharmacokinetic interaction has been seen between ropinirole and domperidone (a medicinal product used to treat nausea and vomiting) that would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood-brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these medicinal products with ropinirole should be avoided. Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP 1A2. A pharmacokinetic study (with a ropinirole dose of 2mg, three times a day) revealed that ciprofloxacin increased the Cmax and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP 1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

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Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these medicinal products with ropinirole should be avoided.

4.6 Pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). As the potential risk for humans is unknown, it is recommended that ropinirole is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

4.7 Effects on ability to drive and use machines

Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1,000, <1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Use of ropinirole in Restless Legs Syndrome

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

Table 2 lists the adverse drug reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole.

Table 2 Adverse drug reactions reported in 12-week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307)

Psychiatric disorders	
Common	Nervousness
Uncommon	Confusion
Nervous system disorders	
Common	Syncope, somnolence, dizziness (including vertigo)
Vascular disorders	
Uncommon	Postural hypotension, hypotension
Gastrointestinal disorders	
Very common	Vomiting, nausea
Common	Abdominal pain
General disorders and administration site conditions	
Common	Fatigue

Hallucinations were reported uncommonly in the open label long-term studies.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Management of undesirable effects

Dose reduction should be considered if patients experience significant undesirable effects. If the undesirable effect abates, gradual up-titration can be re-instituted. Anti-nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

Other experience with ropinirole

Ropinirole is also indicated for the treatment of Parkinson's disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

Psychiatric disorders	
Common	Hallucinations, confusion
Uncommon	Increased libido
Nervous system disorders	
Very common	Syncope, dyskinesia, somnolence
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
General disorders and administration site conditions	
Common	Leg oedema

Post marketing reports

Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Impulse control disorders including pathological gambling andn hypersexuality, and increase libido, have been reported (see section 4.4).

In Parkinson’s disease, ropinirole is associated with somnolence and has been associated uncommonly (>1/1,000, <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000).

Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe.

Very rare cases of hepatic reactions (<1/10,000), mainly increase of liver enzymes, have been reported.

4.9 Overdose

It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Clinical efficacy

VUNEXIN should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

In the four 12-week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12-week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, $p<0.0001$; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

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

Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36-week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, $p=0.0156$).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12-week placebo-controlled studies, indicated that ropinirole-treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0-100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; $p<0.0001$), sleep quantity (0.7 hours, 95% CI 0.49, 0.94); $p<0.0001$), sleep adequacy (18.6, 95% CI 13.77, 23.45; $p<0.0001$) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; $p<0.0001$).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7-10 days after withdrawal of therapy were higher in ropinirole-treated patients than in placebo-treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole-treated patients.

In clinical studies most patients were of Caucasian origin.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with C_{max} reached on average 1.5 hours after the dose. In the presence of food, C_{max} is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination

Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

Linearity

The pharmacokinetics of ropinirole are linear overall (C_{max} and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics

In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible.

In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug: behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation. In the albino rat only, retinal degeneration was observed in a long term study at a high dose (50 mg/kg), probably associated with an increased exposure to light.

Genotoxicity: Genotoxicity was not observed in the usual battery of *in vitro* and *in vivo* tests.

Carcinogenicity: From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg there was no evidence of any carcinogenic effect in the mouse. In the rat, the only drug-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-Coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above +25°C

Store in the original package.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.

Packs of 28 or 84 tablets, consisting of blister strips of 14 tablets or
packs of 84 consisting of blister strips of 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glaxo Smithkline (Ireland) Limited
Stonemasons Way
Rathfarnham
Dublin 16

8 MARKETING AUTHORISATION NUMBER

PA 1077/107/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st December 2006

10 DATE OF REVISION OF THE TEXT

August 2007