IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1327/012/003
Case No: 2049379

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

Orion Corporation

Orionintie 1, **FI-02200 Espoo**, **Finland**

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

Pramipexole Orion 0.35 mg 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 **19/03/2010** until **18/03/2015**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pramipexole Orion 0.35 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pramipexole Orion 0.35 mg tablets contain 0.35 mg of pramipexole base
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, biconvex, oblong, scored on both sides tablets (dimensions: 11.1mm × 5.6mm approximately).

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pramipexole Orion is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone 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).

4.2 Posology and method of administration

Parkinson’s disease

The tablets should be taken orally, swallowed with water, and can be taken either with or without food. The daily dosage is administered in equally divided doses 3 times a day.

Initial treatment:
Dosages should be increased gradually from a starting-dose of 0.264 mg of base (0.375 mg of salt) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable side-effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Ascending – Dose Schedule of Pramipexole Orion				
Week	Dosage (mg of base)	Total Daily Dose (mg of base)	Dosage (mg of salt)	Total Daily Dose (mg of salt)
1	3 x 0.088	0.264	3 x 0.125	0.375
2	3 x 0.18	0.54	3 x 0.25	0.75
3	3 x 0.35	1.1	3 x 0.5	1.50

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.1 mg base (1.5 mg salt) (see section 4.8).

Maintenance treatment:
The individual dose should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in three pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of undesirable effects. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, doses higher than 1.1 mg (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole Orion, depending on reactions in individual patients.

Treatment discontinuation:
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4).

Dosing in patients with renal impairment:
The elimination of pramipexole is dependent on renal function. The following dosage schedule is suggested for initiation of therapy:

- Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose.
- In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of Pramipexole Orion should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily).
- In patients with a creatinine clearance less than 20 ml/min, the daily dose of Pramipexole Orion should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily.

If renal function declines during maintenance therapy, reduce Pramipexole Orion daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the Pramipexole Orion daily dose by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min, and as a single daily dose if creatinine clearance is less than 20 ml/min.

Dosing in patients with hepatic impairment
Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been investigated.

Dosing in children and adolescents
Pramipexole Orion is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

When prescribing Pramipexole Orion in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2.

Hallucinations
Hallucinations are known as a side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur.

Dyskenesia
In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of Pramipexole Orion. If they occur, the dose of levodopa should be decreased.

Sudden onset of sleep and somnolence
Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Pramipexole Orion.
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. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.7 and section 4.8).

Impulse control disorders and compulsive behaviours
Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Furthermore, patients and caregivers should be aware of the fact that behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/taper discontinuation should be considered.

Patients with psychotic disorders
Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks.
Coadministration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5).

Ophthalmologic monitoring
Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.

Severe cardiovascular disease
In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

Neuroleptic malignant syndrome
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

Augmentation
Reports in the literature indicate that treatment with dopaminergic medications can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The frequency of augmentation after longer use of pramipexole and the appropriate management of these events have not been evaluated in controlled clinical trials.

4.5 Interaction with other medicinal products and other forms of interaction

Plasma protein binding
Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway
Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules.

Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine and amantadine, may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole Orion.

Combination with levodopa
When Pramipexole Orion is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage of other anti-parkinsonian medication is kept constant while increasing the dose of Pramipexole Orion.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole.

Antipsychotic medicinal products
Coadministration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

4.6 Pregnancy and lactation

The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3). Pramipexole Orion should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma.
In the absence of human data, Pramipexole Orion should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Pramipexole Orion has major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole Orion 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 recurrent episodes and somnolence have resolved (see also sections 4.4 , 4.5 and 4.8).

4.8 Undesirable effects

The following adverse reactions are expected under the use of Pramipexole Orion:
Abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; confusion, constipation, delusion, dizziness, dykinesia, fatigue, hallucinations, headache, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pruritus and rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, visual disturbance including vision blurred and visual acuity reduced, vomiting, weight decrease, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on pramipexole and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63 % of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials. The adverse drug-reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. However, the majority of common adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was continued.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

very common (≥ 1/10);

common (≥ 1/100, < 1/10);

uncommon (≥ 1/1,000, < 1/100);

rare (≥ 1/10,000, < 1/1,000);

very rare (< 1/10,000);
not known (cannot be estimated from the available data)

Parkinson's disease, most common adverse events
The most commonly (≥ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.2). More frequent adverse drug reactions in combination with levodopa were dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson's disease

System Organ Class	Adverse Drug Reaction
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions; confusion, hallucinations, insomnia, restlessness
Uncommon	Compulsive shopping, delusion, hypersexuality, libido disorder, paranoia, pathological gambling
Not known	binge eating, hyperphagia
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	amnesia headache
Uncommon	hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual disturbance including vision blurred and visual acuity reduced
Vascular disorders	
Very common	hypotension
Gastrointestinal disorders	
Very Common	nausea
Common	Constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash

General disorders and administration site conditions	
Common	fatigue, peripheral oedema
Investigations	
Common	Weight decrease
Uncommon	Weight increase

The most commonly (≥ 5%) reported adverse drug reactions in patients treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with pramipexole (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).

Table 2: Other indication

System Organ Class	Adverse Drug Reaction
Psychiatric disorders	
Common	abnormal dreams, insomnia
Uncommon	confusions, hallucinations, libido disorder, restlessness
Not known	behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; delusion, hyperphagia, paranoia
Nervous system disorders	
Common	dizziness, headache, somnolence
Uncommon	sudden onset of sleep, syncope
Not known	amnesia, dyskinesia, hyperkinesia
Eye disorders	
Uncommon	visual disturbance including vision blurred and visual acuity reduced
Vascular disorders	
Uncommon	hypotension
Gastrointestinal disorders	
Very common	Nausea
Common	Constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue
Uncommon	peripheral oedema
Investigations	
Uncommon	weight decrease, weight increase

Somnolence

Pramipexole is associated with somnolence (8.6%) and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (0.1%). See also section 4.4.

Pramipexole may be associated with libido disorders (increased (0.1%) or decreased (0.4%)).

Impulse control disorders and compulsive behaviours
Patients treated with dopamine agonists for Parkinson's disease, including pramipexole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. See also section 4.4.

In a cross-sectional, retrospective screening and case-control study including 3090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤ 65 years), not being married and self-reported family history of gambling behaviours.

4.9 Overdose

There is no clinical experience with massive overdosage. The expected adverse events would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: dopamine agonists, ATC code: N04B C05

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 D_3 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.

In human volunteers, a dose-dependent decrease in prolactin was observed.

Clinical trials in Parkinson's disease

In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Controlled clinical trials included approximately 2100 patients of Hoehn and Yahr stages I – IV. Out of these, approximately 900 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, efficacy of pramipexole in the controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration**,** initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson´s disease.

5.2 Pharmacokinetic properties

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 1 and 3 hours. Concomitant administration with food did not reduce the extent of pramipexole absorption, but the rate of absorption was reduced. Pramipexole shows linear kinetics and a small inter-patient variation of plasma levels.

In humans, the protein binding of pramipexole is very low (< 20%) and the volume of distribution is large (400 l). High brain tissue concentrations were observed in the rat (approx. 8-fold compared to plasma).

Pramipexole is metabolised in man only to a small extent.

Renal excretion of unchanged pramipexole is the major route of elimination. Approximately 90% of ^{14}C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400 ml/min. The elimination half-life (t½) varies from 8 hours in the young to 12 hours in the elderly.

5.3 Preclinical safety data

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Maize starch
Hydroxypropylcellulose
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

30 months

6.4 Special precautions for storage

Store in the original package in order to protect from light.

This medicinal product does not require any special temperature storage conditions

6.5 Nature and contents of container

10 tablets per OPA/Aluminium/PVC/Aluminium blister strips.
Cartons containing 3 or 10 blister strips.

Pack sizes: 30, 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA 1327/12/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th March 2010

10 DATE OF REVISION OF THE TEXT