Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pipexus 3.15 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 4.5 mg pramipexole dihydrochloride monohydrate equivalent to 3.15 mg pramipexole.

Please note:
Pramipexole doses as published in the literature refer to the salt form.
Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

The round tablets of 11 mm diameter are white or nearly white, have a flat surface with bevelled edges and are marked with 315 on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pipexus is indicated in adults 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).

4.2 Posology and method of administration

Pipexus prolonged-release tablets are a once-a-day oral formulation of pramipexole.

Initial treatment
Doses should be increased gradually from a starting dose of 0.26 mg of base (0.375 mg of salt) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of Pipexus prolonged-release tablets		
Week	**Daily dose (mg of base)**	**Daily dose (mg of salt)**
1	0.26	0.375
2	0.52	0.75
3	1.05	1.5

If a further dose increase is necessary the daily dose should be increased by 0.52 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.15 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 1.05 mg of base (1.5 mg of salt) per day (see section 4.8).

Patients already taking pramipexole tablets may be switched to Pipexus prolonged-release tablets overnight, at the same daily dose. After switching to Pipexus prolonged-release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.26 mg of base (0.375 mg of salt) to a maximum of 3.15 mg of base (4.5 mg of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.05 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.05 mg of base (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.05 mg of base (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 dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Pipexus, depending on reactions in individual patients (see section 4.5).

Missed dose
When the intake of a dose is missed, Pipexus prolonged-release tablets should be taken within 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time.

Treatment discontinuation
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Pramipexole should be tapered off at a rate of 0.52 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.52 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.26 mg of base (0.375 mg of salt) per day (see section 4.4).

Renal impairment
The elimination of pramipexole is dependent on renal function. The following dose schedule is suggested:
Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 30 and 50 ml/min, treatment should be started with 0.26 mg Pipexus prolonged-release tablets every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week. If a further dose increase is necessary, doses should be increased by 0.26 mg pramipexole base at weekly intervals up to a maximum dose of 1.57 mg pramipexole base (2.25 mg of salt) per day.

The treatment of patients with a creatinine clearance below 30 ml/min with Pipexus prolonged-release tablets is not recommended as no data are available for this patient population. The use of pramipexole tablets should be considered.

If renal function declines during maintenance therapy, the recommendations given above should be followed.

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 Pipexus pharmacokinetics has not been investigated.

Paediatric population
The safety and efficacy of Pipexus in children below 18 years has not been established. There is no relevant use of Pipexus prolonged-release tablets in the paediatric population for the indication of Parkinson's Disease.

Method of administration
The tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When prescribing Pipexus 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.

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

Dystonia
Axial dystonia including antecollis, camptocormia and pleurothotonus (Pisa Syndrome) has occasionally been reported in patients with Parkinson's disease following initiation or incremental dose increase of pramipexole. Although dystonia may be a symptom of Parkinson's disease, the symptoms in these patients have improved after reduction or withdrawal of pramipexole. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment in the dose of pramipexole considered.

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 Pipexus. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of the dose 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 sections 4.5, 4.7 and section 4.8).

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Pipexus. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Mania and delirium
Patients should be regularly monitored for the development of mania and delirium. Patients and carers should be made aware that mania and delirium can occur in patients treated with pramipexole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Patients with psychotic disorders
Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration 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).

Dopamine agonist withdrawal syndrome

To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off (see section 4.2). Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain, which may be severe. Patients should be informed about this before tapering the dopamine agonist and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the pramipexole dose temporarily (see section 4.8).

Remnants in stool
Some patients have reported the occurrence of remnants in faeces which may resemble intact pramipexole prolonged-release tablets. If patients report such an observation, the physician should reassess patient's response to therapy.

4.5 Interaction with other medicinal products and other forms of interactions

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, amantadine, mexiletine, zidovudine, cisplatin, quinine and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pipexus.

Combination with levodopa
When Pipexus is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of Pipexus.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.4, 4.7 and 4.8).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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). Pipexus should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
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, Pipexus should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

Fertility

No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected oestrous cycles and reduced female fertility as expected for a dopamine agonist. However, these studies did not indicate direct or indirect harmful effects with respect to male fertility.

4.7 Effects on ability to drive and use machines

Pipexus can have a major influence on the ability to drive and use machines.
Hallucinations or somnolence can occur.

Patients being treated with Pipexus 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

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,778 Parkinson's disease patients on pramipexole and 1,297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% of patients on placebo reported at least one adverse drug reaction.

The majority of adverse drug reactions usually start early in therapy and most tend to disappear even as therapy is 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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

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 pramipexole salt per day (see section 4.2). A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia
Endocrine disorders	
Uncommon	inappropriate antidiuretic hormone secretion[1]
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions; confusion, hallucinations, insomnia
Uncommon	binge eating[1], compulsive shopping, delusion, hyperphagia[1], hypersexuality, libido disorder, paranoia, pathological gambling, restlessness, delirium
Rare	mania
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	headache
Uncommon	amnesia, hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual impairment including diplopia, vision blurred and visual acuity reduced
Cardiac disorders	
Uncommon	cardiac failure[1]
Vascular disorders	
Common	hypotension
Respiratory, thoracic, and mediastinal disorders	
Uncommon	dyspnoea, hiccups

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
Not known	dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.
Investigations	
Common	weight decrease including decreased appetite
Uncommon	weight increase

[1]This side effect has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 2,762 patients with Parkinson's Disease treated with pramipexole.

Description of selected adverse reactions

Somnolence

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

Libido disorders

Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including pramipexole. (See section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 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.

Dopamine agonist withdrawal syndrome

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain (see section 4.4).

Cardiac failure

In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole (observed risk ratio 1.86; 95% CI, 1.21-2.85).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no clinical experience with massive overdose. The expected adverse reactions 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 overdose 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: anti-Parkinson drugs, dopamine agonists, ATC code: N04BC05.

Mechanism of action

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.

Pharmacodynamic effects

In human volunteers, a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where pramipexole prolonged-release tablets were titrated faster (every 3 days) than recommended up to 3.15 mg pramipexole base (4.5 mg of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Clinical efficacy and safety in Parkinson's disease

In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Placebo-controlled clinical trials included approximately 1,800 patients of Hoehn and Yahr stages I – V treated with pramipexole. Out of these, approximately 1,000 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 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.

The safety and efficacy of pramipexole prolonged-release tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of three randomised, controlled trials. Two trials were conducted in patients with early Parkinson's disease and one trial was conducted in patients with advanced Parkinson's disease.

Superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (CGI-I and PGI-I responder rates) efficacy endpoints in a double-blind placebo-controlled trial including a total of 539 patients with early Parkinson's disease. Maintenance of efficacy was shown in patients treated for 33 weeks. Pramipexole prolonged-release tablets were non-inferior to pramipexole immediate release tablets as assessed on the UPDRS Parts II+III score at week 33.

In a double-blind placebo-controlled trial including a total of 517 patients with advanced Parkinson's disease who were on concomitant levodopa therapy superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (off-time) efficacy endpoints.

The efficacy and tolerability of an overnight switch from pramipexole tablets to pramipexole prolonged-release tablets at the same daily dose were evaluated in a double-blind clinical study in patients with early Parkinson's disease.

Efficacy was maintained in 87 of 103 patients switched to pramipexole prolonged-release tablets. Out of these 87 patients, 82.8% did not change their dose, 13.8% increased and 3.4% decreased their dose.
In half of the 16 patients who did not meet the criterion for maintained efficacy on UPDRS Part II+III score, the change from baseline was considered not clinically relevant.

Only one patient switched to pramipexole prolonged-release tablets experienced a drug-related adverse event leading to withdrawal.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with pramipexole in all subsets of the paediatric population in Parkinson's Disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Pramipexole is completely absorbed following oral administration. The absolute bioavailability is greater than 90%.

In a Phase I trial, where pramipexole immediate release and prolonged-release tablets were assessed in fasted state, the minimum and peak plasma concentration (C^{min}, C^{max}) and exposure (AUC) of the same daily dose of pramipexole prolonged-release tablets given once daily and pramipexole tablets given three times a day were equivalent.

The once daily administration of pramipexole prolonged-release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of pramipexole immediate release tablets.

The maximum plasma concentrations occur at about 6 hours after administration of pramipexole prolonged-release tablets once daily. Steady state of exposure is reached at the latest after 5 days of continuous dosing.

Concomitant administration with food does generally not affect the bioavailability of pramipexole. Intake of a high fat meal induced an increase in peak concentration (C^{max}) of about 24% after a single dose administration and about 20% after multiple dose administrations and a delay of about 2 hours in time to reach peak concentration in healthy volunteers. Total exposure (AUC) was not affected by concomitant food intake. The increase in C^{max} is not considered clinically relevant. In the Phase III studies that established safety and efficacy of pramipexole prolonged-release tablets, patients were instructed to take study medication without regard to food intake.

While body weight has no impact on the AUC, it was found to influence the volume of distribution and therefore the peak concentrations C^{max}. A decreased body weight by 30 kg results in an increase in $C_{max}$of 45%. However, in Phase III trials in Parkinson's disease patients no clinically meaningful influence of body weight on the therapeutic effect and tolerability of pramipexole prolonged-release tablets was detected.

Pramipexole shows linear kinetics and a small inter-patient variation of plasma levels.

Distribution
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).

Biotransformation
Pramipexole is metabolised in man only to a small extent.

Elimination
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.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

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

Hypromellose
Calcium hydrogen phosphate, anhydrous
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister Al/OPA-Al-PVC: 10, 30 and 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Macarthys Laboratories Limited
T/A Martindale Pharmaceuticals
Bampton Road
Harold Hill
Romford RM3 8UG

United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0274/003/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th September 2016

10 DATE OF REVISION OF THE TEXT

July 2018