APPROVED PACKAGE INSERT:

SCHEDULING STATUS: **S4**

PROPRIETARY NAME (and dosage form):

Pexola® 0,125 mg tablets
Pexola® 0,25 mg tablets
Pexola® 1,0 mg tablets

COMPOSITION:
PEXOLA 0,125 mg: Pramipexole dihydrochloride monohydrate 0,125 mg equivalent to pramipexole 0,088 mg/tablet.
PEXOLA 0,25 mg: Pramipexole dihydrochloride monohydrate 0,25 mg equivalent to pramipexole 0,18 mg/tablet.
PEXOLA 1,0 mg: Pramipexole dihydrochloride monohydrate 1,0 mg equivalent to pramipexole 0,70 mg/tablet.
Inactive ingredients: anhydrous colloidal silica, magnesium stearate, maize starch, mannitol and povidone.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION:
A 5.4.1 Anti-Parkinsonism preparations

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties: Pramipexole is a dopamine agonist and binds with high selectivity and specificity to the dopamine D2 subfamily receptors and has preferential affinity to D3 receptors; it has full intrinsic activity.

The precise mechanism of action of pramipexole in the treatment for Parkinson's disease is unknown; it is believed to be related to its ability to stimulate dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release and turnover.

In a clinical trial with healthy volunteers, where PEXOLA was titrated faster than recommended (every 3 days) up to 4,5 mg per day, an increase in blood pressure and heart rate was observed.

The precise mechanism of action of pramipexole as a treatment for Restless Legs Syndrome is not known. The pathophysiology of Restless Legs Syndrome is largely unknown.

Pharmacokinetic properties: Pramipexole is rapidly and almost completely absorbed following oral administration. The absolute bioavailability is greater than 90 % and the maximum plasma concentrations occur between 1 and 3 hours. The rate of absorption is reduced by food intake but not the overall extent of absorption. 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 (approximately 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 and accounts for about 80 % of the dose. Approximately 90 % of a 14C-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.
Pramipexole clearance correlates well with creatinine clearance. Pramipexole clearance is about 75 % lower in severe renal impairment, and 60 % lower in moderate renal impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

INDICATIONS:
PEXOLA is indicated in the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa.

PEXOLA is indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome.

CONTRA-INDICATIONS:
Hypersensitivity to pramipexole or any of the components of PEXOLA.
PEXOLA is not recommended for use in children below 18 years of age.
Severe renal impairment (CrCl < 30 ml/min).

WARNINGS:

Falling asleep during activities of daily living:
Patients treated with PEXOLA have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on PEXOLA, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving PEXOLA at doses above 1,5 mg/day. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with PEXOLA, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with PEXOLA such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g. cimetidine – see INTERACTIONS). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g. conversations, eating, etc.), PEXOLA should ordinarily be discontinued. If a decision is made to continue PEXOLA, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Patients and caregivers should be aware of the fact that abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours) such as binge eating, compulsive shopping, hypersexuality and pathological gambling have been reported in patients treated with dopaminergic medicines including PEXOLA. Dose reduction/tapered discontinuation should be considered.

INTERACTIONS:
Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of PEXOLA in healthy volunteers (N=10). PEXOLA did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa Cmax by about 40 % and a decrease in Tmax from 2,5 to 0,5 hours.

Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of PEXOLA.

Amantadine: The interaction has not been examined, however, an interaction is possible via the same system of excretion in the kidney.

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50 % increase in PEXOLA AUC and a 40 % increase in half-life (N=12).

Other medicines eliminated via renal secretion: Population pharmacokinetic analysis suggests that co-administration of medicines that are secreted by the cationic transport system (e.g. cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine and quinine) decreases the clearance of PEXOLA by about 20 %, while those secreted by the anionic transport system (e.g. cephalosporins, penicillins, indomethacin, hydrochlorothiazide and chlorpropamide) are likely to have little effect on the clearance of PEXOLA.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect PEXOLA elimination because PEXOLA is not appreciably metabolised by these enzymes *in vivo* or *in vitro*. PEXOLA does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1 and CYP34A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that PEXOLA will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1,5 mg three times a day).

Dopamine antagonists: Since PEXOLA is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of PEXOLA.

Other anti-Parkinsonian medication: While increasing the dose of PEXOLA it is recommended that the dosage of levodopa is reduced and the dosage of other anti-Parkinsonian medication kept constant.

Alcohol and sedatives: Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with PEXOLA and when taking concomitant medication that increases plasma levels of pramipexole (e.g. cimetidine).

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been shown.

Patients should be advised to notify their medical practitioners if they become pregnant or intend to become pregnant during therapy.

As PEXOLA treatment inhibits secretion of prolactin in humans inhibition of lactation is expected. Consequently, PEXOLA should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:
Parkinson's disease:
The tablets should be taken orally, swallowed with water, and can be taken with or without food.

The daily dosage is administered in equally divided doses 3 times per day.

Initial treatment: The dosage schedule shown below is suggested which may require usage of other strengths within the range of PEXOLA tablets.

As shown below, dosages should be increased gradually from a starting dose of 0,375 mg 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 PEXOLA		
Week	**Dosage (mg)**	**Total daily dose (mg)**
1	3 x 0,125	0,375
2	3 x 0,25	0,75
3	3 x 0,5	1,50

If a further dose increase is necessary the daily dose should be increased by 0,75 mg at weekly intervals up to a maximum dose of 4,5 mg per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1,5 mg/day (see **WARNINGS**).

Maintenance treatment: The individual dose should be in the range of 0,375 mg to a maximum of 4,5 mg per day.
During dose escalation in three pivotal studies, both in early and advanced disease, efficacy was observed starting at a daily dose of 1,5 mg. This does not preclude that in individual patients doses higher than 1,5 mg per day can result in additional therapeutic benefit.
This applies particularly to patients with advanced disease where a reduction of the levodopa therapy is intended.

Treatment discontinuation: PEXOLA should be tapered off over several days.

Dosing in patients with concomitant levodopa therapy: In patients with concomitant levodopa therapy it is recommended that the dosage of levodopa is reduced during both dose escalation and maintenance treatment with PEXOLA. This may be necessary in order to avoid excessive dopaminergic stimulation.

Dosing in patients with renal impairment: The elimination of PEXOLA 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 or dosing frequency.

In patients with creatinine clearance between 30 and 50 ml/min, the initial daily dose of PEXOLA should be administered in two divided doses starting at 0,125 mg twice a day (0,25 mg daily). A maximum daily dose of 2,25 mg pramipexole dihydrochloride monohydrate should not be exceeded.

PEXOLA is contra-indicated in patients with creatinine clearance less than 30 ml/min.

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

Dosing in patients with hepatic impairment: Dose reduction is not considered necessary in patients with hepatic impairment.

Restless Legs Syndrome (RLS):
The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

The recommended starting dose of PEXOLA is 0,125 mg taken once daily 2 - 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 - 7 days to a maximum of 0,75 mg per day (as shown in the table below):

Ascending-Dose Schedule of PEXOLA	
Titration Step	**Once Daily Evening Dose (mg)**
1	0,125
2*	0,25
3*	0,50
4*	0,75
* if needed	

Treatment discontinuation: PEXOLA can be discontinued without tapered dose reduction.

Dosing in patients with renal impairment: The elimination of PEXOLA is dependent on renal function and closely related to the creatinine clearance. Based on a pharmacokinetic study in renally impaired subjects, patients with a creatinine clearance above 30 ml/min require no reduction in daily dose. The use of PEXOLA in RLS patients with renal impairment has not been studied.

Dosing in patients with hepatic impairment: Dose reduction is not considered necessary in patients with hepatic impairment, as approx. 90 % of absorbed drug is excreted through the kidneys.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects:
Frequency classes: 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).

Parkinson's disease:
Infections and infestations:
Uncommon: Pneumonia.

Psychiatric disorders:
Common: Abnormal behaviour (reflecting symptoms of impulse control disorders and compulsions), hallucinations, confusion, insomnia, abnormal dreams, restlessness.
Uncommon: Compulsive shopping, pathological gambling, hypersexuality, delusion, paranoia, libido disorders (increase or decrease).
Reported but frequencies unknown: Binge eating, hyperphagia.

Nervous system disorders:
Very common: Dizziness, dyskinesia, somnolence.
Common: Headache, amnesia.
Uncommon: Falling asleep during activities of daily living/sudden onset of sleep (see **WARNINGS**), hyperkinesia, syncope.

Eye disorders:
Common: Visual disturbance including vision blurred and visual acuity reduced.

Vascular disorders:
Very common: Hypotension.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea.

Gastrointestinal disorders:
Very common: Nausea.
Common: Constipation, vomiting.

Skin and subcutaneous tissue disorders:
Uncommon: Hypersensitivity, pruritus, rash.

General disorders:
Common: Peripheral oedema and fatigue.

Investigations:
Common: Weight decrease.
Uncommon: Weight increase.

Adverse events: Relationship to age, gender and race: Among the treatment-emergent adverse events in patients treated with PEXOLA, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. Only a small percentage (4 %) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Restless Legs Syndrome (RLS):
Infections and infestations:
Reported but frequencies unknown: Pneumonia.

Psychiatric disorders:
Common: Insomnia, abnormal dreams.
Uncommon: Confusion, libido disorders (increase or decrease), hallucinations, restlessness.

Reported but frequencies unknown: Abnormal behaviour (reflecting symptoms of impulse control disorders and compulsions), pathological gambling, delusion, binge eating, hyperphagia, compulsive shopping, hypersexuality, paranoia.

Nervous system disorders:
Common: Dizziness, somnolence, headache.
Uncommon: Falling asleep during activities of daily living/sudden onset of sleep, dyskinesia, syncope.
Reported but frequencies unknown: Hyperkinesia, amnesia.

Eye disorders:
Uncommon: Visual disturbance including vision blurred and visual acuity reduced.

Vascular disorders:
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea.

Gastrointestinal disorders:
Very common: Nausea.
Common: Constipation, vomiting.

Skin and subcutaneous tissue disorders:
Uncommon: Hypersensitivity, pruritus, rash.

General disorders:
Common: Fatigue.
Uncommon: Peripheral oedema.

Investigations:
Uncommon: Weight increase, weight decrease.

Post marketing experience:
In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of PEXOLA tablets, primarily in Parkinson's disease patients. Similar types of events were grouped into a smaller number of standardised categories using MedDRA dictionary: abnormal behaviour, abnormal dreams, accidents (including fall), blackouts, compulsive shopping, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, pruritus, syncope, vomiting and weight increase.

Special Precautions:
Patients should be instructed to take PEXOLA only as prescribed.

Patients and caregivers should be aware of the fact that abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours) such as binge eating, compulsive shopping, hypersexuality and pathological gambling have been reported in patients treated with dopaminergic medicines including PEXOLA. Dose reduction/tapered discontinuation should be considered.

Symptomatic hypotension: Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with PEXOLA.

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension especially during dose escalation, and should be informed of this risk.

In clinical trials of PEXOLA however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to PEXOLA than among those assigned to placebo.
While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded. In individual patients, hypotension may occur at the beginning of treatment, especially if titration of PEXOLA is too fast.

In case of severe cardiovascular disease, particular 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.

Hallucinations and confusion: Patients should be informed that hallucinations and confusion can occur and that the elderly are at higher risk than younger patients.

In placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9 % (35 of 388) of patients receiving PEXOLA tablets, compared with 2,6 % (6 of 235) of patients receiving placebo. In the placebo-controlled trials in advanced Parkinson's disease, where patients received PEXOLA and concomitant levodopa, hallucinations were observed in 16,5 % (43 of 260) of patients receiving PEXOLA, compared with 3,8 % (10 of 264) of patients receiving placebo.

Hallucinations were of sufficient severity to cause discontinuation of treatment in 3,1 % of the early Parkinson's disease patients and 2,7 % of the advanced Parkinson's disease patients compared with about 0,4 % of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to PEXOLA. In the early Parkinson's disease patients, the risk of hallucinations was 1,9 times greater than placebo in patients younger than 65 years and 6,8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3,5 times greater than placebo in patients younger than 65 years and 5,2 times greater than placebo in patients older than 65 years.

Within the RLS clinical development program for registration, one case of hallucinations has been reported.

Renal: Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing PEXOLA tablets to patients with renal insufficiency (see **DOSAGE AND DIRECTIONS FOR USE** and **CONTRA-INDICATIONS**).

Dyskinesia: PEXOLA may potentiate the dopaminergic side-effects of levodopa and may cause or exacerbate pre-existing dyskinesia. Decreasing the dose of levodopa may ameliorate this side-effect.

Nausea: If patients develop nausea, they should be advised that taking PEXOLA with food may reduce the occurrence of nausea.

Laboratory tests: During the development of PEXOLA, no systemic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Ophthalmic: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. Evaluation of the retinas of albino mice, pigmented rats, monkeys and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e. disk shedding) may be involved.

Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk than the general population. Whether the further increased risk observed was due to Parkinson's disease or other factors, such as medicines used to treat Parkinson's disease such as PEXOLA, is unclear.
For the reasons stated above, patients and providers are advised to monitor for melanoma when using PEXOLA.

Treatment discontinuation in Parkinson's disease: Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy such as PEXOLA.

Augmentation in RLS: Reports in the literature indicate treatment of RLS with dopaminergic medications such as PEXOLA 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 controlled trials of PEXOLA in patients with RLS were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of PEXOLA and the appropriate management of these events have not been evaluated in controlled clinical trials.

PEXOLA tablets contain mannitol. This may have a mild laxative effect.

Effects on ability to drive and use machines: Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.

Patients should be alerted to the potential sedating effects associated with PEXOLA, including somnolence and the possibility of falling asleep while engaged in activities of daily living.

Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor operate other complex machinery until they have gained sufficient

experience with PEXOLA to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their medical practitioner.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Symptoms: There is no clinical experience with massive overdosage. The expected adverse events should be related to the pharmacodynamic profile of a dopamine agonist including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension.

Therapy: 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 and electrocardiogram monitoring. Haemodialysis has not been shown to be helpful.

IDENTIFICATION:
PEXOLA 0,125 mg: Flat, round, white tablets with bevelled edges and markings: one face P6; other face Company symbol.
PEXOLA 0,25 mg: White, oval tablets, both faces flat, with bevelled edges and markings: one face P7/deep breakline/P7; other face Company symbol/breakline/Company symbol.
PEXOLA 1,0 mg: Flat, round, white tablets with bevelled edges and markings: one face P9/deep breakline/P9; other face Company symbol/breakline/Company symbol.

PRESENTATION:
Cartons containing 100 tablets packed in aluminium blister strips of 10 tablets per strip.

STORAGE INSTRUCTIONS:
PEXOLA tablets should be stored below 30 °C in the original blisters until required. Once removed from the packaging, the tablets should be protected from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
PEXOLA 0,125 mg: 32/5.4.1/0298
PEXOLA 0,25 mg: 32/5.4.1/0299
PEXOLA 1,0 mg: 32/5.4.1/0300

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Ingelheim Pharmaceuticals (Pty) Ltd
Pine Avenue
Randburg
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DATE OF PUBLICATION OF THIS PACKAGE INSERT:
19 April 2013