SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

Pexola® ER 0,375 mg extended release tablets
Pexola® ER 0,75 mg extended release tablets
Pexola® ER 1,5 mg extended release tablets
Pexola® ER 3,0 mg extended release tablets

COMPOSITION:

PEXOLA ER 0,375 mg: Pramipexole dihydrochloride monohydrate 0,375 mg/extended release tablet.
PEXOLA ER 0,75 mg: Pramipexole dihydrochloride monohydrate 0,75 mg/extended release tablet.
PEXOLA ER 1,5 mg: Pramipexole dihydrochloride monohydrate 1,5 mg/extended release tablet.
PEXOLA ER 3,0 mg: Pramipexole dihydrochloride monohydrate 3,0 mg/extended release tablet.

Inactive ingredients: anhydrous colloidal silica, carbomer, magnesium stearate, maize starch and hypromellose.
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 pramipexole extended release tablets were titrated faster than recommended (every 3 days) up to 4,5 mg per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Pharmacokinetic properties:

The maximum plasma concentrations after administration of PEXOLA ER occur at about 6 hours. Generally, food does not affect the bioavailability of pramipexole. An increase of about 20 % in peak concentration and a delay of about 2 hours in time to reach peak concentration when PEXOLA ER was taken after a high fat meal has been observed compared to fasting intake.

Pramipexole after multiple dosing of the extended release formulation shows dose proportional kinetics.

In humans the protein binding of pramipexole is 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 (< 10 %).

Renal excretion of unchanged pramipexole is the major route of elimination. 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 plasma clearance correlates 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 ER 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.

CONTRAINDICATIONS:

Hypersensitivity to pramipexole or any of the components of PEXOLA ER.
Not recommended for use in children below 18 years of age.
Moderate to severe renal impairment (creatinine clearance less than 50 mL/min).

WARNINGS:

Falling asleep during activities of daily living:
Patients treated with PEXOLA ER 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 ER, 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 ER 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 ER, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with PEXOLA ER 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 ER should ordinarily be discontinued. If a decision is made to continue PEXOLA ER, 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 ER. Dose reduction/tapered discontinuation should be considered.

Dopamine Dysregulation Syndrome (DDS):
Dopamine dysregulation syndrome (DDS) has been observed in some patients during treatment with PEXOLA ER. This is an addictive disorder that results in the excessive use of this or other dopaminergic medicinal products. Before the start of treatment, patients and caregivers must be warned about the potential risk of developing DDS (see ***Side effects***).

INTERACTIONS:

Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of PEXOLA ER in healthy volunteers (N=10). PEXOLA ER 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 ER.

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 ER 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 ER 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 ER.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect PEXOLA ER elimination because PEXOLA ER is not appreciably metabolised

by these enzymes *in vivo* or *in vitro*. PEXOLA ER 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 ER will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (4,5 mg/day).

Dopamine antagonists: Since PEXOLA ER 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 ER.

Other anti-Parkinsonian medication: While increasing the dose of PEXOLA ER 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 ER 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 ER treatment inhibits secretion of prolactin in humans inhibition of lactation is expected. Consequently, PEXOLA ER should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

PEXOLA ER should be taken once daily at about the same time each day. PEXOLA ER should be swallowed whole with water, and must not be chewed, divided or crushed. PEXOLA ER may be taken with or without food.

When the intake of a dose is missed, PEXOLA ER may be taken up to 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.

Initial treatment:

Dosages should be increased gradually from a starting dose of 0,375 mg per day and then increased every 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 ER extended release tablets		
Week	**Total daily dose (mg)**	**Extended release tablets (mg)**
1	0,375	0,375
2	0,75	0,75
3	1,50	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.

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

Patients already taking pramipexole immediate release tablets may be switched to PEXOLA ER extended release tablets overnight, at the same daily dose.

Maintenance treatment: The individual maintenance dose ranges from 0,375 mg to a maximum of 4,5 mg per day.
During dose escalation in pivotal studies, both in early and advanced Parkinson's disease, efficacy was observed starting at a daily dose of 1,5 mg.
However doses lower than 1,5 mg per day can have adequate therapeutic benefit.

Treatment discontinuation: PEXOLA ER tablets should be tapered off at a rate of 0,75 mg per day until the daily dose has been reduced to 0,75 mg. Thereafter the dose should be reduced by 0,375 mg per day.

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 ER. This may be necessary in order to avoid excessive dopaminergic stimulation.

Dosing in patients with renal impairment: The elimination of pramipexole dihydrochloride monohydrate 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.
Inadequate data is available for the treatment of patients with a creatinine clearance below 50 mL/min with PEXOLA ER extended release tablets (See **CONTRAINDICATIONS**).

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:
Frequency classes:
Derived from clinical trial data pertaining to the extended release formulation: 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 available data).

Infections and infestations:
Not known: Pneumonia.

Psychiatric disorders:
Common: Abnormal behaviour (including symptoms of impulse control disorders and compulsions), insomnia, hallucinations.

Uncommon: Libido disorders (increase or decrease), hypersexuality, compulsive shopping, pathological gambling, delusion, confusion, abnormal dreams, restlessness.
Not known: Paranoia, binge eating, hyperphagia, dopamine dysregulation syndrome.
Dopamine dysregulation syndrome (DDS) is an addictive disorder that has been observed in some patients treated with PEXOLA ER. Patients affected exhibit the compulsive abuse of dopaminergic medicinal products, using higher doses than are necessary for the adequate control of motor symptoms from Parkinson's disease. In some cases, this may result in severe dyskinesia (see also **WARNINGS**).

Nervous system disorders:
Very common: Somnolence.
Common: Headache, dizziness, dyskinesia.
Uncommon: Falling asleep during activities of daily living/sudden onset of sleep (see **WARNINGS**), syncope.
Not known: Amnesia, hyperkinesia.

Eye disorders:
Common: Visual impairment including diplopia, vision blurred and visual acuity reduced.

Vascular disorders:
Common: Hypotension.

Respiratory, thoracic and mediastinal disorders:
Not known: Dyspnoea, hiccups.

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

Skin and subcutaneous tissue disorders:
Uncommon: Hypersensitivity, pruritus.
Not known: Rash.

General disorders:
Common: Peripheral oedema and fatigue.

Investigations:
Common: Weight decrease including decreased appetite.
Not known: Weight increase.

Post-marketing experience:
The following adverse reactions have been identified during post-approval use of immediate-release pramipexole tablets, primarily in Parkinson's disease patients: Abnormal behaviour, abnormal dreams, accidents (including fall), blackouts, cardiac failure, 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.
In a pharmacoepidemiological study, pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole.

Special Precautions:
Patients should be instructed to take PEXOLA ER 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 PEXOLA ER. 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. 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 ER.

PEXOLA ER in clinical studies and clinical experience appears 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 PEXOLA ER ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension especially during dose escalation, and should be informed of this risk.

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 PEXOLA ER.

Hallucinations and confusion: Hallucinations and confusion are known side effects of treatment with PEXOLA ER in Parkinson's disease patients. Hallucinations were more frequent when PEXOLA ER was given in combination with levodopa in Parkinson's disease patients with advanced disease than in monotherapy in Parkinson's disease patients with early disease. Patients should be informed that (mostly visual) hallucinations can occur.

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 pramipexole 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 pramipexole and concomitant levodopa, hallucinations were observed in 16,5 % (43 of 260) of patients receiving pramipexole, 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 pramipexole. 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.

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

Dyskinesia: PEXOLA ER 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.

Laboratory tests: During the development of PEXOLA ER, 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 PEXOLA ER, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanoma when using PEXOLA ER.

Treatment discontinuation: Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy, including PEXOLA ER.

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 ER, 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 ER 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 with PEXOLA ER, 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 ER 0,375 mg extended release tablets: White to off white, round, biconvex, bevel-edged tablets. One side is debossed with the code P1, the other side is debossed with the Boehringer Ingelheim company symbol.
PEXOLA ER 0,75 mg extended release tablets: White to off white, round, biconvex, bevel-edged tablets. One side is debossed with the code P2, the other side is debossed with the Boehringer Ingelheim company symbol.
PEXOLA ER 1,5 mg extended release tablets: White to off white, oval, biconvex tablets. One side is debossed with the code P3, the other side is debossed with the Boehringer Ingelheim company symbol.
PEXOLA ER 3,0 mg extended release tablets: White to off white, oval, biconvex tablets. One side is debossed with the code P4, the other side is debossed with the Boehringer Ingelheim company symbol.

PRESENTATION:

PEXOLA ER extended release tablets are packed in silver aluminium/aluminium blisters of 10 tablets per strip. Cartons contain 30 tablets.

STORAGE INSTRUCTIONS:

PEXOLA ER extended release tablets should be stored at or below 30 °C in the original blisters until required.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

PEXOLA ER 0,375 mg extended release tablets: 43/5.4.1/1062
PEXOLA ER 0,75 mg extended release tablets: 43/5.4.1/1063
PEXOLA ER 1,5 mg extended release tablets: 43/5.4.1/1064
PEXOLA ER 3,0 mg extended release tablets: 43/5.4.1/1065

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa

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