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APPROVED PROFESSIONAL INFORMATION NOVEMBER 2025

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PEXSON 0.375 XR (tablet)

PEXSON 0.75 XR (tablet)

PEXSON 1.5 XR (tablet)

PEXSON 3 XR (tablet)

PEXSON 4.5 XR (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEXSON 0.375 XR: Each Extended release tablet contains pramipexole 0,375 mg of pramipexole dichloride.

Contains Sugar (Mannitol 12.025 mg)

PEXSON 0.75 XR: Each Extended release tablet contains pramipexole 0,75 mg of pramipexole dichloride.

Contains Sugar (Mannitol 11.650 mg)

PEXSON 1.5 XR: Each Extended release tablet contains pramipexole 1,5 mg of pramipexole dichloride.

Contains Sugar (Mannitol 10.900 mg)

PEXSON 3 XR: Each Extended release tablet contains pramipexole 3 mg of pramipexole dichloride.

Contains Sugar (Mannitol 9.400 mg)

PEXSON 4.5 XR: Each Extended release tablet contains pramipexole 4,5 mg of pramipexole dichloride.

Contains Sugar (Mannitol 14.100 mg)

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For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Extended release tablet

PEXSON 0.375 XR: White coloured, circular, flat, beveled edged, uncoated tablet debossed 'ER 1' on one side of the tablet and '0.375' on other side.

PEXSON 0.75 XR: White coloured, circular, flat, beveled edged, uncoated tablet debossed 'ER 2' on one side of the tablet and '0.75' on other side.

PEXSON 1.5 XR: White coloured, oval shaped, biconvex, uncoated tablet debossed 'ER 3' on one side of the tablet and '1.5' on other side.

PEXSON 3 XR : White coloured, oval shaped, biconvex, uncoated tablet debossed 'ER 5' on one side of the tablet and '3.0' on other side.

PEXSON 4.5 XR: White coloured, oval shaped, biconvex, uncoated tablet debossed 'ER 7' on one side of the tablet and '4.5' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEXSON XR 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.

4.2 Posology and method of administration

Posology

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 PEXSON XR extended release tablets		
Week	**Dosage (mg)**	**Total daily dose (mg)**

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1	0,375 mg	0,375
2	0,75 mg	0,75
3	1,50 mg	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 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 section 4.4)

Patients already taking pramipexole immediate release tablets may be switched to **PEXSON XR** 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:

PEXSON XR 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 **PEXSON XR.** This may be necessary in order to avoid excessive dopaminergic stimulation.

Special populations:

Renal impairment:

The elimination of **PEXSON XR** 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

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mL/min with **PEXSON XR** extended release tablets (see section 4.3).

Hepatic impairment:

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

Method of administration

PEXSON XR should be taken once daily at about the same time each day. **PEXSON XR** should be swallowed whole with water, and must not be chewed, divided or crushed.

May be taken with or without food.

When the intake of a dose is missed, **PEXSON XR** 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.

4.3 Contraindications

PEXSON XR is contraindicated:

- In patients with a history of hypersensitivity to the active substance pramipexole or to any of the excipients listed in 6.1.
- **PEXSON XR** is not recommended for use in children below 18 years of age.
- Moderate to severe renal impairment (creatinine clearance less than 50 mL/min).

4.4 Special warnings and precautions for use

When prescribing **PEXSON XR** 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 **PEXSON XR**. 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 less frequently. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with **PEXSON XR**. 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 **PEXSON XR**. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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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 medicines 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 (DAWS)

DAWS has been reported with dopamine agonists, including pramipexole (see section 4.8). To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off (see section 4.2). Limited data suggests that patients with impulse control disorders and those receiving high daily dose and/or high cumulative doses of dopamine agonists may be at higher risk for developing DAWS. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating and pain and do not respond to levodopa. Prior to tapering off and discontinuing pramipexole, patients should be informed about potential withdrawal symptoms. Patients should be closely monitored during tapering and discontinuation. In case of severe

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and/or persistent withdrawal symptoms, temporary re administration of pramipexole at the lowest effective dose may be considered.

Dopamine Dysregulation Syndrome (DDS):

Dopamine dysregulation syndrome (DDS) has been observed in some patients during treatment with **PEXSON XR**. 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 *section 4.8*).

Remnants in stool

Some patients have reported the occurrence of remnants in faeces which may resemble intact **PEXSON XR** prolonged-release tablets. If patients report such an observation, the medical practitioner should reassess patient's response to therapy.

4.5 Interaction with other medicines 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 medicines 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 caused a 50 % increase in the pramipexole AUC and a 40 % increase in half-life. Therefore, medicines that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, ranitidine, diltiazem, triamterene, verapamil, quinidine and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicines are administered concomitantly with **PEXSON XR**.

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Combination with levodopa/carbidopa

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

CYP interactions:

Inhibitors of cytochrome P450 enzymes would not be expected to affect **PEXSON XR** elimination because **PEXSON XR** is not appreciably metabolised by these enzymes *in vivo* or *in vitro*. **PEXSON XR** 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 **PEXSON XR** will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (4,5 mg/day).

Dopamine antagonists*:*

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

Other anti-Parkinsonian medication:

While increasing the dose of **PEXSON XR** 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 **PEXSON XR** and when taking concomitant medication that increases plasma levels of pramipexole (e.g. cimetidine).

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Antipsychotic medicines

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

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

Breastfeeding

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

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

PEXSON XR can have a major influence on the ability to drive and use machines.

Hallucinations, dizziness, visual impairment or somnolence can occur.

Patients being treated with **PEXSON XR** 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).

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4.8 Undesirable effects

Summary of the safety profile

The majority of adverse drug reactions usually start early in therapy and most tend to disappear even as therapy is continued.

The most frequently reported adverse drug reaction in patients with Parkinson's disease were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue.

Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations			Pneumonia
Endocrine disorders		Inappropriate antidiuretic hormone secretion	
Psychiatric disorders	Insomnia, hallucinations, behavioural symptoms of impulse disorders and compulsions	Compulsive shopping, pathological gambling, hypersexuality, delusion, libido disorder, delirium, mania, abnormal dreams, confusion, restlessness	Paranoia, binge eating, hyperphagia, dopamine dysregulation syndrome. Dopamine dysregulation syndrome (DDS) is an addictive disorder that has been observed in

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			some patients treated with pramipexole. Patients affected exhibit the compulsive abuse of dopaminergic medicines, 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
Nervous system disorders	Somnolence, dizziness, dyskinesia, headache,	Sudden onset of sleep, syncope	Amnesia, hyperkinesia
Eye disorders	Visual impairment including diplopia, vision blurred, visual acuity reduced		

Cardiac disorders			Cardiac failure
Vascular disorders	Hypotension		

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Respiratory, thoracic and mediastinal disorders			Dyspnoea, hiccups
Gastrointestinal disorders	Constipation, nausea, vomiting		
Skin and subcutaneous disorders		Hypersensitivity, pruritis	rash
General disorders and administration site conditions	Fatigue, peripheral oedema		Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain
Investigations	Weight decrease including decreased appetite		Weight increase

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers

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are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com

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.

Treatment

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, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

Haemodialysis has not been shown to be helpful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.5.4.1 Anti-Parkinsonism preparations

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.

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5.2 Pharmacokinetic properties

Absorption

Pramipexole is 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.

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 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 ($t_{½}$) 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 section 4.2).

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Hypromellose

Pregelatinized starch

Carbomer homopolymer

Colloidal silicon dioxide

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for blister pack and 24 months for container pack.

6.4 Special precautions for storage

Store at or below 30°C for blister pack and

Store at or below 25°C for container pack

Protect from moisture.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in a round white 60 HDPE container with a silica gel sachet and closed with a white child resistant closure packed in an outer carton. Pack sizes include 28's, 30's tablets.

Tablets are packed in aluminium foil laminated on one side and laminated to PVC on the other side. Pack sizes include 28's tablets or 30's tablets.

Not all pack sizes may be marketed.

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6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

PEXSON XR 0.375 mg: 58/5.4.1/0016

PEXSON XR 0.75 mg: 58/5.4.1/0017

PEXSON XR 1.5 mg: 58/5.4.1/0018

PEXSON XR 3 mg: 58/5.4.1/0019

PEXSON XR 4.5 mg: 58/5.4.1/0020

9. DATE OF FIRST AUTHORISATION

PEXSON XR: 25/11/2025

10. DATE OF REVISION OF THE TEXT

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