1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEXASP 0,125 mg tablets

PEXASP 0,25 mg tablets

PEXASP 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEXASP 0,125 mg:

Each PEXASP 0,125 mg tablet contains 0,125 mg pramipexole as pramipexole dihydrochloride monohydrate.

Contains sugar: Mannitol 41,55 mg

PEXASP 0,25 mg:

Each PEXASP 0,25 mg tablet contains 0,25 mg pramipexole as pramipexole dihydrochloride monohydrate.

Contains sugar: Mannitol 41,55 mg

PEXASP 1 mg:

Each PEXASP 1 mg tablet contains 1 mg pramipexole as pramipexole dihydrochloride monohydrate

Contains sugar: Mannitol 41,55 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

PEXASP 0,125 mg arewhite, round tablets, marked on one side with a “0” (zero).

PEXASP 0,25 mg are white, round tablets, marked on one side with a “1” (one), scored on the other side.

PEXASP 1 mg are white, round tablets, marked on one side with a “3” (three), scored on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEXASP is indicated for:

- The treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa.

- The symptomatic treatment of idiopathic Restless Legs Syndrome (RLS).

4.2 Posology and method of administration

Posology

Parkinson's disease

The tablets should be taken orally, swallowed with water and can be taken either with or without food.

The daily dose is administered in equally divided doses three times a day.

Initial treatment

The dosage schedule shown below is suggested, which may require usage of other strengths within the range of PEXASP tablets.

As shown below dosages should be increased gradually from a starting dose of 0,375 mg per day and then increased every 5 to 7 days. Provided patients do not experience intolerable side

effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Ascending-Dose Schedule of PEXASP		
Week	Dosage (mg)	Total daily dose (m)
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 to a maximum daily dose of 4,50 mg. It is important to note however that the incidence of somnolence is increased at daily doses of more than 1,50 mg (see section 4.4).

Maintenance treatment

The individual dose should be in the range of 0,375 mg to a maximum of 4,50 mg per day. During dose escalation, both in early and advance disease, efficacy was observed starting at a daily dose of 1,50 mg. This does not preclude that in individual patients' doses higher then 1,50 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

PEXASP should be tapered off over several days in the treatment of Parkinson's disease.

Dosing in patients on concomitant levodopa therapy

It is recommended that the dose of levodopa is reduced during both dose escalation and

maintenance treatment with PEXASP to avoid excessive dopaminergic stimulation (see section 4.4 and section 4.5).

Dosing in patients with renal impairment

The elimination of PEXASP is dependent on renal function. The following dosage schedule is recommended 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 PEXASP 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.

PEXASP is contraindicated in patients with creatinine clearance less than 30 mL/min (see section 4.3).

If renal function declines during maintenance therapy, reduce PEXASP by the same percentage as the decrease in creatinine clearance i.e. if creatinine clearance declines by 30 %, then reduce the PEXASP 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 PEXASP is 0,125 mg taken once daily 2 to 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 to 7 days to a maximum of 0,75 mg per day (as shown in the table below)

Ascending-dose schedule of PEXASP

Titration step	Once daily evening dose (mg)
1	0,125
2*	0,25
3*	0,50
4*	0,75
*if needed	

Treatment discontinuation

PEXASP can be discontinued without tapered dose reduction in Restless Legs Syndrome.

Dosing in patients with renal impairment

Dosing in patients with renal impairment: The elimination of PEXASP 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 PEXASP 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 approximately 90 % of absorbed medicine is excreted through the kidneys.

Method of administration

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

4.3 Contraindications

PEXASP is contraindicated in:

- Patients with hypersensitivity to the active ingredient or to any of the excipients in PEXASP (see section 6.1).
- Use in children below 18 years of age.

- Severe renal impairment (CrCl < 30 mL/min).

4.4 Special warnings and precautions for use

Falling asleep during activities of daily living:

Patients treated with pramipexole, as in PEXASP 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 pramipexole as in PEXASP, 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 PEXASP at doses above 1,50 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 PEXASP, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with PEXASP such as concomitant sedating medicines, the presence of sleep disorders, and concomitant medicines that increase pramipexole plasma levels (e.g. cimetidine - see

section 4.5).

If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g. conversations, eating, etc.), PEXASP should ordinarily be discontinued. If a decision is made to continue PEXASP, 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.

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 PEXASP to gauge whether or not it affects their mental and/or motor performance adversely (see section 4.7).

Impulse control disorders

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 PEXASP. Dose reduction/tapered discontinuation should be considered (see section 4.2).

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder that has been observed in some patients treated with PEXASP. 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 (see below).

Symptomatic hypotension (Orthostatic 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 at the initiation of treatment with PEXASP.

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 pramipexole however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to pramipexole 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 PEXASP is too fast.

Renal impairment

Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing PEXASP tablets to patients with renal insufficiency (see section 4.2 and 4.3)

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

Hallucinations and confusion

Hallucinations and confusion can occur with the use of PEXASP and the elderly are at higher risk than younger patients.

Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa (see section 4.8). Patients should be informed that (mostly visual) hallucinations can occur.

Age appears to increase the risk of hallucinations attributable to PEXASP. Data suggested that 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.

Dyskinesia

In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of PEXASP (see section 4.8). PEXASP may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate pre-existing dyskinesia. If this occurs, the dose of levodopa should be decreased (see section 4.5).
Decreasing the dose of levodopa may ameliorate this side effect.

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, as in PEXASP. Although dystonia may be a symptom of Parkinson's disease, the symptoms in these patients have improved after reduction or withdrawal of pramipexole, as in PEXASP. If dystonia occurs, the dopaminergic medicines regimen should be reviewed and an adjustment in the dose of PEXASP considered.

Mania and delirium

Patients should be regularly monitored for the development of mania and delirium. Patients and caregivers should be made aware that mania and delirium can occur in patients treated with PEXASP. 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 PEXASP should be avoided (see section 4.5).

Ophthalmologic monitoring

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

Nausea

Patients should be advised to take PEXASP with food to reduce the occurrence of nausea.

Treatment discontinuation in Parkinson's disease

The abrupt withdrawal of dopaminergic therapy, may lead to symptoms suggestive of a neuroleptic malignant syndrome (NMS) (see section 4.2 and 4.8)

Laboratory tests

No systemic abnormalities on routine laboratory testing have been documented for pramipexole as in PEXASP, 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.

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

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 PEXASP, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanoma when using PEXASP.

Augmentation

Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicines 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. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Augmentation was observed in 11,8 % of patients in the pramipexole group (N = 152) and 9,4 % of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between pramipexole and placebo groups.

The controlled trials of PEXASP in patients with RLS were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of PEXASP and the appropriate management of these events have not been evaluated in controlled clinical trials.

Patients should be alerted to the potential sedating effects associated with PEXASP, including somnolence and the possibility of falling asleep while engaged in activities of daily living (see Boxed Warnings)

Paediatric population

Safety and efficacy of PEXASP in children has not been established and it is therefore not

recommended for use in children under the age of 18 years (see section 4.3).

Excipients

PEXASP contains mannitol and may have a mild laxative effect.

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; however, PEXASP may increase peak plasma concentration of levodopa and exacerbate dyskinesias. A reduction of the dose of levodopa is recommended (see section 4.3).

Other *anti-Parkinson* medicines

Requires that the dose of the other medicines remain unchanged (except for levodopa as above) while the dose of PEXASP is increased.

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, medicines that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, ranitidine, diltiazem, verapamil, triamterene, 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 medicines are administered concomitantly with PEXASP.

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 PEXASP 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 PEXASP.

Combination with levodopa

When PEXASP is given in combination with levodopa, it is recommended that the dose of levodopa is reduced, and the dose of other anti-Parkinsonian medicines is kept constant while increasing the dose of PEXASP.

CYP interactions

Inhibitors of cytochrome P450 enzymes would not be expected to affect PEXASP elimination because PEXASP is not appreciably metabolised by these enzymes *in vivo* or *in vitro*. PEXASP 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 PEXASP will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1,5 mg three times a day).

Antipsychotics (Dopamine antagonists)

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

Alcohol and sedatives

Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with PEXASP and when taking concomitant medication that increases plasma levels of pramipexole (e.g. cimetidine) (see sections 4.4, 4.7 and 4.8)

None of the following medications have been associated with a pharmacokinetic interaction with PEXASP

Carbidopa/levodopa, selegiline, amantadine, probenecid, inhibitors of cytochrome P450 enzymes.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy

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

The effect on pregnancy and lactation has not been investigated in humans.

Breastfeeding

Pramipexole may be excreted in breastmilk. PEXASP should not be used during breastfeeding. The excretion of pramipexole into breast milk has not been studied in women.

Fertility

No studies on the effect of human fertility has been conducted.

4.7 Effects on ability to drive and use machines

PEXASP has a major influence on the ability to drive and use machines.

Since adverse reactions such as hallucinations, somnolence and visual disturbances have been reported in patients receiving PEXASP, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain PEXASP does not adversely affect their ability to do so (see section 4.4 and 4.8).

4.8 Undesirable effects

a) *Summary of the safety profile*

Parkinson's disease

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse reactions were frequently reported for both groups. 63% of patients on pramipexole and 52 % of patients on placebo reported at least one adverse reaction. The majority of adverse reactions usually start early in therapy and most tend to disappear even as therapy is continued.

Parkinson's disease, most common adverse reactions

The most commonly (≥ 5 %) reported adverse 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 reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Restless Legs Syndrome

The most commonly (≥ 5 %) reported adverse reactions in patients with Restless Legs Syndrome treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with pramipexole (20,8 % and 10,5 %, respectively) compared to males (6,7 % and 7,3 %, respectively).

b)Tabulated list of adverse reactions

Table 1: Parkinson's disease

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Infections and infestations	Urinary tract infection	Pneumonia,	
Endocrine disorders		Inappropriate antidiuretic hormone secretion[1]	
Psychiatric disorders	Insomnia, confusional state, delusions, dream abnormalities, hallucination, paranoid reaction, sleep disorders, thinking abnormalities, visual hallucination, increased or decreased libido, abnormal behaviour (reflecting symptoms of impulse control disorders and compulsions),	Pathological gambling, binge eating[1], compulsive shopping, hyperphagia, hypersexuality, restlessness, delirium, mania, hyperphagia[1]	Hyperphagia, dopamine dysregulation syndrome.
Nervous system disorders	Dizziness, dyskinesia, extrapyramidal syndrome, somnolence, akathisia, dystonia, gait abnormalities, headache, hypertonia, hypoesthesia, myoclonus, taste perversions, amnesia,	Hyperkinesia, syncope, excessive daytime somnolence, falling asleep during activities of daily living/sudden onset of sleep	
Eye disorders	Accommodation abnormalities, conjunctivitis, lacrimation disorders, visual abnormalities, diplopia, vision blurred, visual acuity reduced		
Ear and labyrinth disorders	Tinnitus		
Vascular disorders	Postural hypotension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, rhinitis, sinusitis, hiccups		
Gastrointestinal disorders	Constipation, nausea, vomiting, anorexia, dry mouth, dyspepsia, dysphagia, flatulence, tooth disease		
Skin and subcutaneous tissue disorders	Pruritus, sweating, skin disorders, rash, hypersensitivity		

Musculoskeletal and connective tissue disorders	Arthritis, bursitis, leg cramps, myasthenia, twitching		
Renal and urinary disorders	Urinary frequency, urinary incontinence, urinary tract infection		
Reproductive system and breast disorders	Impotence		
General disorders and administrative site conditions	Asthenia, accidental injury, chest pain, fatigue, malaise, fever, general and peripheral oedema		
Investigations	Increased creatine PK, decreased weight	Increased weight	

[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.

Table 2: Restless Legs Syndrome

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Pneumonia[1]	
Endocrine disorders		Inappropriate antidiuretic hormone secretion[1]	
Psychiatric disorders	Insomnia abnormal dreams	Restlessness, confusion hallucinations libido disorder delusion[1] hyperphagia[1] paranoia[1] mania[1]	

		delirium[1] behavioural symptoms of impulse control disorders and compulsions[1] (such as: compulsive shopping, pathological gambling, hypersexuality, binge eating)	
Nervous system disorders	Headache, dizziness, somnolance	Sudden onset of sleep, syncope, dyskinesia,amnesia[1],hyperkinesia[1],	
Eye disorders		Visual impairment including visual acuity reduced diplopia vision blurred	
Cardiac disorders		Cardiac failure[1]	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, hiccups	
Gastrointestinal disorders	Nausea, constipation, vomiting		
Skin and subcutaneous tissue disorders		Hypersensitivity, pruritus, rash	
General disorders and administrative 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	

[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 1,395 patients with Restless Legs Syndrome treated with pramipexole

c) Description of selected adverse reactions

Parkinson's disease

Relationship to age, gender and race

Among the treatment-emergent adverse events in patients treated with PEXASP, 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 treated with pramipexole

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 PEXASP (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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

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, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.4.1 Anti-Parkinson medicines

Pharmacotherapeutic group: Medicines affecting autonomic function. Cholinolytics (anticholinergics).

ATC code: N04BC05

Mechanism of action

Pramipexole is a dopamine agonist and binds with high selectivity and specificity for the dopamine D_2 subfamily dopamine receptors and has preferential affinity to D_3 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 by binding to these receptors, it is thought that pramipexole can stimulate dopamine activity on the nerves of the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release and turnover.

In a clinical trial with healthy volunteers, where pramipexole 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.

5.2 Pharmacokinetics properties

Absorption

Pramipexole is rapidly and almost completely absorbed following oral administration.

Distribution

Protein binding in humans is low (<20 %) and volume of distribution (V_D) is large (400 L). High brain tissue concentrations were observed in the rat (approximately 8-fold compared to plasma.

Biotransformation

The absolute bioavailability is greater than 90 %, indicating that it is well absorbed and undergoes little presystemic metabolism. In the presence of food, the rate of absorption is reduced but not the extent of absorption. Maximum plasma concentrations are reached in 1 to 3 hours.

Pramipexole is minimally metabolised in humans.

Elimination

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 ($t_{1/2}$) varies from 8 hours in the young and 12 hours in the elderly.

Pramipexole clearance correlates well with creatinine clearance. Clearance of pramipexole is reduced in moderate to severe renal impairment. Pramipexole clearance is about 75 % lower in severe renal impairment, and 60 % lower in moderate renal impairment (see section 4.2).

Linearity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, mannitol, microcrystalline cellulose (pH 102), povidone K30, purified talc, starch partially pregelatinised.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep blister in carton until required for use

6.5 Nature and contents of container

100 tablets are packed in polyvinylchloride blister strips sealed with an aluminium foil and polyamide film (OPA) backing. There are 10 tablets per blister strip and ten strips are packed into an outer cardboard carton together with a leaflet.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBER

PEXASP 0,125 mg: 42/5.4.1/1023

PEXASP 0,25 mg: 42/5.4.1/1022

PEXASP 1 mg: 42/5.4.1/1024

9. DATE OF FIRST AUTHORISATION

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PEXASP 0,25 mg: 16 February 2017

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10. DATE OF REVISION OF THE TEXT

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