ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.088 mg tablets
Oprymea 0.18 mg tablets
Oprymea 0.35 mg tablets
Oprymea 0.7 mg tablets
Oprymea 1.1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oprymea 0.088 mg tablets
Each tablet contains 0.088 mg pramipexole (as 0.125 mg pramipexole dihydrochloride monohydrate).

Oprymea 0.18 mg tablets
Each tablet contains 0.18 mg pramipexole (as 0.25 mg pramipexole dihydrochloride monohydrate).

Oprymea 0.35 mg tablets
Each tablet contains 0.35 mg pramipexole (as 0.5 mg pramipexole dihydrochloride monohydrate).

Oprymea 0.7 mg tablets
Each tablet contains 0.7 mg pramipexole (as 1 mg pramipexole dihydrochloride monohydrate).

Oprymea 1.1 mg tablets
Each tablet contains 1.1 mg pramipexole (as 1.5 mg pramipexole dihydrochloride monohydrate).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Oprymea 0.088 mg tablets
White, round, with bevelled edges and imprint "P6" on one side of the tablet.

Oprymea 0.18 mg tablets
White, oval, with bevelled edges, both sides scored, with imprint "P7" on both halves of one side of the tablet. The tablet can be divided into equal doses.

Oprymea 0.35 mg tablets
White, oval, with bevelled edges, both sides scored, with imprint "P8" on both halves of one side of the tablet. The tablet can be divided into equal doses.

Oprymea 0.7 mg tablets
White, round, with bevelled edges, both sides scored, with imprint "P9" on both halves of one side of the tablet. The tablet can be divided into equal doses.

Oprymea 1.1 mg tablets
White, round, with bevelled edges, both sides scored. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oprymea is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

Oprymea is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt) (see section 4.2).

4.2 Posology and method of administration

Posology

Parkinson’s disease

The daily dose is administered in equally divided doses 3 times a day.

Initial treatment
Doses should be increased gradually from a starting-dose of 0.264 mg of base (0.375 mg of salt) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending – Dose Schedule of Oprymea				
Week	Dose (mg of base)	Total Daily Dose (mg of base)	Dose (mg of salt)	Total Daily Dose (mg of salt)
1	3 x 0.088	0.264	3 x 0.125	0.375
2	3 x 0.18	0.54	3 x 0.25	0.75
3	3 x 0.35	1.1	3 x 0.5	1.50

If a further dose increase is necessary the daily dose should be increased by 0.54 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg (of salt) per day (see section 4.8).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg of base (1.5 mg of salt). In advanced Parkinson’s disease, pramipexole doses higher than 1.1 mg of base (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Oprymea, depending on reactions in individual patients (see section 4.5).

Treatment discontinuation
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome or a dopamine agonist withdrawal syndrome. Pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4). Dopamine agonist withdrawal syndrome could still appear while tapering and a temporary increase of the dose could be necessary before resuming tapering (see section 4.4).

Renal impairment
The elimination of pramipexole is dependent on renal function. The following dose 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 a creatinine clearance between 20 and 50 ml/min, the initial daily dose of Oprymea should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily). A maximum daily dose of 1.57 mg pramipexole base (2.25 mg of salt) should not be exceeded.

In patients with a creatinine clearance less than 20 ml/min, the daily dose of Oprymea should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily. A maximum daily dose of 1.1 mg pramipexole base (1.5 mg of salt) should not be exceeded.

If renal function declines during maintenance therapy the Oprymea daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then the Oprymea daily dose should be reduced by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min, and as a single daily dose if creatinine clearance is less than 20 ml/min.

Hepatic impairment
Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on Oprymea pharmacokinetics has not been investigated.

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

Restless Legs Syndrome

The recommended starting dose of Oprymea is 0.088 mg of base (0.125 mg of salt) 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 0.54 mg of base (0.75 mg of salt) per day (as shown in the table below).

Dose Schedule of Oprymea		
Titration Step	Once Daily Evening Dose (mg of base)	Once Daily Evening Dose (mg of salt)
1	0.088	0.125
2*	0.18	0.25
3*	0.35	0.50
4*	0.54	0.75

* if needed

Patient's response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Treatment discontinuation
Since the daily dose for the treatment of Restless Legs Syndrome will not exceed 0.54 mg of base (0.75 mg of salt) Oprymea can be discontinued without tapering off. In a 26 week placebo controlled trial, rebound of RLS symptoms (worsening of symptom severity as compared to baseline) was

observed in 10% of patients (14 out of 135) after abrupt discontinuation of treatment. This effect was found to be similar across all doses.

Renal impairment
The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose.
The use of pramipexole has not been studied in haemodialysis patients, or in patients with severe renal impairment.

Hepatic impairment
Dose adjustment in patients with hepatic failure is not required, as approx. 90% of absorbed active substance is excreted through the kidneys.

Paediatric population
Oprymea is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Tourette Disorder

Paediatric population
Oprymea is not recommended for use in children and adolescents below 18 years since the efficacy and safety has not been established in this population. Oprymea should not be used in children or adolescents with Tourette Disorder because of a negative benefit-risk balance for this disorder (see section 5.1).

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

When prescribing Oprymea 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 Oprymea. If they occur, the dose of levodopa should be decreased.

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

Sudden onset of sleep and somnolence
Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without

awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Oprymea. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of 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 pramipexole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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

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

Coadministration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5).

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

Severe cardiovascular disease
In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

Neuroleptic malignant syndrome
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

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

Augmentation

Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products 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.

4.5 Interaction with other medicinal products 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 medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway
Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine,amantadine mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Oprymea.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3). Oprymea should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma. In the absence of human data, Oprymea should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

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

4.7 Effects on ability to drive and use machines

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

Hallucinations or somnolence can occur.

Patients being treated with Oprymea and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5, and 4.8).

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63 % of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

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

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data .

Parkinson's disease, most common adverse reactions
The most commonly (≥5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg pramipexole salt per day (see section 4.2). A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson's disease

Body System	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known**
Infections and infestations			pneumonia		
Endocrine disorders			inappropriate antidiuretic hormone secretion[1]		
Psychiatric disorders		Insomnia hallucinations abnormal dreams confusion behavioural symptoms of impulse control disorders and compulsions	compulsive shopping pathological gambling restlessness hypersexuality delusion libido disorder paranoia delirium binge eating[1] hyperphagia[1]	mania	
Nervous	somnolence	headache	sudden onset of		

system disorders	dizziness dyskinesia		sleep amnesia hyperkinesia syncope		
Eye disorders		visual impairment including diplopia vision blurred visual acuity reduced			
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 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		

[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.

Restless Legs Syndrome, most common adverse reactions

The most commonly (≥ 5%) reported adverse drug 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 (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).

Table 2: Restless legs syndrome

Body System	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Not known**
Infections and			pneumonia[1]	

infestations				
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 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	

[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.

Description of selected adverse reactions

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

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

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Oprymea (see section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤ 65 years), not being married and self-reported family history of gambling behaviours.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical experience with massive overdose. The expected adverse drug reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdose of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-Parkinson drugs, dopamine agonists, ATC code: N04BC05.

Mechanism of action
Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D_2 subfamily of dopamine receptors of which it has a preferential affinity to D_3 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.

The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

Pharmacodynamic effects
In human volunteers, a dose-dependent decrease in prolactin was observed.

Clinical efficacy and safety in Parkinson's disease

In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson' s disease. Placebo-controlled clinical trials included approximately 1,800 patients of Hoehn and Yahr stages stages I – V treated with pramipexole. Out of these, approximately 1,000 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, efficacy of pramipexole in controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy.

In a controlled double blind clinical trial of 2 year duration**,** initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson´s disease.

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

Clinical efficacy and safety in Restless Legs Syndrome
The efficacy of pramipexole was evaluated in four placebo-controlled clinical trials in approximately 1,000 patients with moderate to very severe idiopathic Restless Legs Syndrome.

The mean change from baseline in the Restless Legs Syndrome Rating Scale (IRLS) and the Clinical Global Impression-Improvement (CGI-I) were the primary efficacy outcome measures. For both primary endpoints statistically significant differences have been observed for the pramipexole dose groups 0.25 mg, 0.5 mg and 0.75 mg pramipexole salt in comparison to placebo. After 12 weeks of treatment the baseline IRLS score improved from 23.5 to 14.1 points for placebo and from 23.4 to 9.4 points for pramipexole (doses combined). The adjusted mean difference was -4.3 points (CI 95% -6.4; -2.1 points, p-value <0.0001). CGI-I responder rates (improved, very much improved) were 51.2% and 72.0% for placebo and pramipexole, respectively (difference 20% CI 95%: 8.1%; 31.8%, p<0.0005). Efficacy was observed with 0.088 mg of base (0.125 mg of salt) per day after the first week of

treatment.

In a placebo-controlled polysomnography study over 3 weeks pramipexole significantly reduced the number of periodic limb movements during time in bed.

Longer term efficacy was evaluated in a placebo-controlled clinical trial. After 26 weeks of treatment, there was an adjusted mean reduction in IRLS total score of 13.7 and 11.1 points in the pramipexole and placebo group, respectively, with a statistically significant (p = 0.008) mean treatment difference of -2.6. CGI-I responder rates (much improved, very much improved) were 50.3% (80/159) and 68.5% (111/162) for placebo and pramipexole, respectively (p = 0.001), corresponding to a number needed to treat (NNT) of 6 patients (95%CI: 3.5, 13.4).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with pramipexole in one or more subsets of the paediatric population in Restless Legs Syndrome (see section 4.2 for information on paediatric use).

Clinical efficacy and safety in Tourette Disorder

The efficacy of pramipexole (0.0625-0.5 mg/day) with paediatric patients aged 6-17 years with Tourette Disorder was evaluated in a 6-week, double-blind, randomised, placebo-controlled flexible dose study. A total of 63 patients were randomised (43 on pramipexole, 20 on placebo). The primary endpoint was change from baseline on the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). No difference was observed for pramipexole as compared to placebo for either the primary endpoint or for any of the secondary efficacy endpoints including YGTSS total score, Patient Global Impression of Improvement (PGI-I), Clinical Global Impression of Improvement (CGI-I), or Clinical Global Impressions of Severity of Illness (CGI-S). Adverse events occurring in at least 5% of patients in the pramipexole group and more common in the pramipexole-treated patients than in patients on placebo were: headache (27.9%, placebo 25.0%), somnolence (7.0%, placebo 5.0%), nausea (18.6%, placebo 10.0%), vomiting (11.6%, placebo 0.0%), upper abdominal pain (7.0%, placebo 5.0%), orthostatic hypotension (9.3%, placebo 5.0%), myalgia (9.3%, placebo 5.0%), sleep disorder (7.0%, placebo 0.0%), dyspnoea (7.0%, placebo 0.0%) and upper respiratory tract infection (7.0%, placebo 5.0%). Other significant adverse events leading to discontinuation of study medication for patients receiving pramipexole were confusional state, speech disorder and aggravated condition (see section 4.2).

5.2 Pharmacokinetic properties

Absorption
Pramipexole is rapidly and 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 ^{14}C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately

400 ml/min. The elimination half-life ($t_{½}$) varies from 8 hours in the young to 12 hours in the elderly.

5.3 Preclinical safety data

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

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

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize starch
Pregelatinised maize starch
Povidone K25
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister pack (Alu/Alu foil): 20, 30, 60, 90 or 100 tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

Oprymea 0.088 mg tablets
20 tablets: EU/1/08/469/001
30 tablets: EU/1/08/469/002
60 tablets: EU/1/08/469/003
90 tablets: EU/1/08/469/004
100 tablets: EU/1/08/469/005

Oprymea 0.18 mg tablets
20 tablets: EU/1/08/469/006
30 tablets: EU/1/08/469/007
60 tablets: EU/1/08/469/008
90 tablets: EU/1/08/469/009
100 tablets: EU/1/08/469/010

Oprymea 0.35 mg tablets
20 tablets: EU/1/08/469/011
30 tablets: EU/1/08/469/012
60 tablets: EU/1/08/469/013
90 tablets: EU/1/08/469/014
100 tablets: EU/1/08/469/015

Oprymea 0.7 mg tablets
20 tablets: EU/1/08/469/016
30 tablets: EU/1/08/469/017
60 tablets: EU/1/08/469/018
90 tablets: EU/1/08/469/019
100 tablets: EU/1/08/469/020

Oprymea 1.1 mg tablets
20 tablets: EU/1/08/469/021
30 tablets: EU/1/08/469/022
60 tablets: EU/1/08/469/023
90 tablets: EU/1/08/469/024
100 tablets: EU/1/08/469/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 September 2008
Date of latest renewal: 9 April 2013

10. DATE OF REVISION OF THE TEXT

July 2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.