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 1.1 mg of base (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). The lowest effective dose should be used (see section 4.4 *Restless legs augmentation syndrome*).

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 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 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.Co-administration 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.

Restless legs augmentation syndrome
Treatment of Restless Legs Syndrome with pramipexole can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The risk of augmentation may increase with higher dose. Prior to treatment, patients should be informed that augmentation may occur and should be advised to contact their physician if they experience symptoms of augmentation. If augmentation is suspected, dose adjustment to the lowest effective dose, or discontinuation of pramipexole should be considered (see section 4.2 and 4.8).

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 system disorders	somnolence dizziness dyskinesia	headache	sudden onset of 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		
Reproductive system and breast disorders				spontaneous penile erection	
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)**	**Rare (≥1/10 000 to <1/1 000)**	**Not known**
Infections and infestations			pneumonia[1]		
Endocrine			inappropriate		

disorders			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	restless legs augmentation syndrome	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		
Reproductive system and breast disorders				spontaneous penile erection	
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 the national reporting system listed in Appendix V.

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 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

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

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg prolonged-release tablets
Oprymea 0.52 mg prolonged-release tablets
Oprymea 1.05 mg prolonged-release tablets
Oprymea 1.57 mg prolonged-release tablets
Oprymea 2.1 mg prolonged-release tablets
Oprymea 2.62 mg prolonged-release tablets
Oprymea 3.15 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oprymea 0.26 mg prolonged-release tablets
Each prolonged-release tablet contains 0.26 mg pramipexole (as 0.375 mg pramipexole dihydrochloride monohydrate).

Oprymea 0.52 mg prolonged-release tablets
Each prolonged-release tablet contains 0.52 mg pramipexole (as 0.75 mg pramipexole dihydrochloride monohydrate).

Oprymea 1.05 mg prolonged-release tablets
Each prolonged-release tablet contains 1.05 mg pramipexole (as 1.5 mg pramipexole dihydrochloride monohydrate).

Oprymea 1.57 mg prolonged-release tablets
Each prolonged-release tablet contains 1.57 mg pramipexole (as 2.25 mg pramipexole dihydrochloride monohydrate).

Oprymea 2.1 mg prolonged-release tablets
Each prolonged-release tablet contains 2.1 mg pramipexole (as 3 mg pramipexole dihydrochloride monohydrate).

Oprymea 2.62 mg prolonged-release tablets
Each prolonged-release tablet contains 2.62 mg pramipexole (as 3.75 mg pramipexole dihydrochloride monohydrate).

Oprymea 3.15 mg prolonged-release tablets
Each prolonged-release tablet contains 3.15 mg pramipexole (as 4.5 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

Prolonged-release tablet

Oprymea 0.26 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P1 on one side, with bevelled edges and possible spots.

Oprymea 0.52 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P2 on one side, with bevelled edges and possible spots.

Oprymea 1.05 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P3 on one side, with bevelled edges and possible spots.

Oprymea 1.57 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P12 on one side, with bevelled edges and possible spots.

Oprymea 2.1 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P4 on one side, with bevelled edges and possible spots.

Oprymea 2.62 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P13 on one side and 262 on the other side, with bevelled edges and possible spots.

Oprymea 3.15 mg prolonged-release tablets
White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P5 on one side and 315 on the other side, with bevelled edges and possible spots.

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).

4.2 Posology and method of administration

Posology

Oprymea prolonged-release tablets are a once-a-day oral formulation of pramipexole.

Initial treatment
Doses should be increased gradually from a starting dose of 0.26 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 prolonged-release tablets		
Week	Daily dose (mg of base)	Daily dose (mg of salt)
1	0.26	0.375
2	0.52	0.75
3	1.05	1.5

If a further dose increase is necessary the daily dose should be increased by 0.52 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.15 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 1.05 mg of base (1.5 mg of salt) per day (see section 4.8).

Patients already taking Oprymea tablets may be switched to Oprymea prolonged-release tablets

overnight, at the same daily dose. After switching to Oprymea prolonged-release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.26 mg of base (0.375 mg of salt) to a maximum of 3.15 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 1.05 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 1.05 mg of base (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.05 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).

Missed dose
When the intake of a dose is missed, Oprymea prolonged-release tablets should be taken within 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.

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 0.52 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.52 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.26 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 30 and 50 mL/min, treatment should be started with 0.26 mg Oprymea prolonged-release tablets every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week. If a further dose increase is necessary, doses should be increased by 0.26 mg pramipexole base at weekly intervals up to a maximum dose of 1.57 mg pramipexole base (2.25 mg of salt) per day.

The treatment of patients with a creatinine clearance below 30 mL/min with Oprymea prolonged-release tablets is not recommended as no data are available for this patient population. The use of Oprymea tablets should be considered.

If renal function declines during maintenance therapy, the recommendations given above should be followed.

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 prolonged-release tablets in the paediatric population for the indication of Parkinson's Disease.

Method of administration
The tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time.

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 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 Oprymea. 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. Co-administration 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.

Remnants in stool
Some patients have reported the occurrence of remnants in faeces which may resemble intact Oprymea prolonged-release tablets. If patients report such an observation, the physician should reassess patient's response to therapy.

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 1 778 Parkinson's disease patients on pramipexole and 1 297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% 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).

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.

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 system disorders	somnolence dizziness dyskinesia	headache	sudden onset of 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		
Reproductive system and breast disorders				spontaneous penile erection	
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.

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 the national reporting system listed in Appendix V.

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.

Management
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 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.

Pharmacodynamic effects
In human volunteers, a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where pramipexole prolonged-release tablets were titrated faster (every 3 days) than recommended up to 3.15 mg pramipexole base (4.5 mg of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

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 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.

The safety and efficacy of pramipexole prolonged-release tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of three randomised, controlled trials. Two trials were conducted in patients with early Parkinson's disease and one trial was conducted in patients with advanced Parkinson's disease.

Superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (CGI-I and PGI-I

responder rates) efficacy endpoints in a double-blind placebo-controlled trial including a total of 539 patients with early Parkinson's disease. Maintenance of efficacy was shown in patients treated for 33 weeks. Pramipexole prolonged-release tablets were non-inferior to pramipexole immediate release tablets as assessed on the UPDRS Parts II+III score at week 33.

In a double-blind placebo-controlled trial including a total of 517 patients with advanced Parkinson's disease who were on concomitant levodopa therapy superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (off-time) efficacy endpoints.

The efficacy and tolerability of an overnight switch from pramipexole tablets to pramipexole prolonged-release tablets at the same daily dose were evaluated in a double-blind clinical study in patients with early Parkinson's disease.

Efficacy was maintained in 87 of 103 patients switched to pramipexole prolonged-release tablets. Out of these 87 patients, 82.8% did not change their dose, 13.8% increased and 3.4% decreased their dose. In half of the 16 patients who did not meet the criterion for maintained efficacy on UPDRS Part II+III score, the change from baseline was considered not clinically relevant.
Only one patient switched to pramipexole prolonged-release tablets experienced a drug-related adverse event leading to withdrawal.

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).

5.2 Pharmacokinetic properties

Absorption
Pramipexole is completely absorbed following oral administration. The absolute bioavailability is greater than 90%.

In a Phase I trial, where pramipexole immediate release and prolonged-release tablets were assessed in fasted state, the minimum and peak plasma concentration (C_{min}, C_{max}) and exposure (AUC) of the same daily dose of pramipexole prolonged-release tablets given once daily and pramipexole tablets given three times a day were equivalent.

The once daily administration of pramipexole prolonged-release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of pramipexole immediate release tablets.

The maximum plasma concentrations occur at about 6 hours after administration of pramipexole prolonged-release tablets once daily. Steady state of exposure is reached at the latest after 5 days of continuous dosing.

Concomitant administration with food does generally not affect the bioavailability of pramipexole. Intake of a high fat meal induced an increase in peak concentration (C_{max}) of about 24% after a single dose administration and about 20% after multiple dose administrations and a delay of about 2 hours in time to reach peak concentration in healthy volunteers. Total exposure (AUC) was not affected by concomitant food intake. The increase in C_{max} is not considered clinically relevant. In the Phase III studies that established safety and efficacy of pramipexole prolonged-release tablets, patients were instructed to take study medication without regard to food intake.

While body weight has no impact on the AUC, it was found to influence the volume of distribution and therefore the peak concentrations C_{max}. A decreased body weight by 30 kg results in an increase in C_{max} of 45%. However, in Phase III trials in Parkinson's disease patients no clinically meaningful influence of body weight on the therapeutic effect and tolerability of pramipexole prolonged-release

tablets was detected.

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 (t½) 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

Hypromellose
Maize starch
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 moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister (OPA/Alu/desiccant/PE-Alu foil): 10, 30, 90 or 100 prolonged-release 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 0.26 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/026
30 prolonged-release tablets: EU/1/08/469/027
90 prolonged-release tablets: EU/1/08/469/028
100 prolonged-release tablets: EU/1/08/469/029

Oprymea 0.52 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/030
30 prolonged-release tablets: EU/1/08/469/031
90 prolonged-release tablets: EU/1/08/469/032
100 prolonged-release tablets: EU/1/08/469/033

Oprymea 1.05 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/034
30 prolonged-release tablets: EU/1/08/469/035
90 prolonged-release tablets: EU/1/08/469/036
100 prolonged-release tablets: EU/1/08/469/037

Oprymea 1.57 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/038
30 prolonged-release tablets: EU/1/08/469/039
90 prolonged-release tablets: EU/1/08/469/040
100 prolonged-release tablets: EU/1/08/469/041

Oprymea 2.1 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/042
30 prolonged-release tablets: EU/1/08/469/043
90 prolonged-release tablets: EU/1/08/469/044
100 prolonged-release tablets: EU/1/08/469/045

Oprymea 2.62 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/046
30 prolonged-release tablets: EU/1/08/469/047
90 prolonged-release tablets: EU/1/08/469/048
100 prolonged-release tablets: EU/1/08/469/049

Oprymea 3.15 mg prolonged-release tablets
10 prolonged-release tablets: EU/1/08/469/050
30 prolonged-release tablets: EU/1/08/469/051
90 prolonged-release tablets: EU/1/08/469/052
100 prolonged-release tablets: EU/1/08/469/053

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

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

1. NAME OF THE MEDICINAL PRODUCT

Treatment initiation pack
Oprymea 0.26 mg prolonged-release tablets
Oprymea 0.52 mg prolonged-release tablets
Oprymea 1.05 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oprymea 0.26 mg prolonged-release tablets
Each prolonged-release tablet contains 0.26 mg pramipexole (as 0.375 mg pramipexole dihydrochloride monohydrate).

Oprymea 0.52 mg prolonged-release tablets
Each prolonged-release tablet contains 0.52 mg pramipexole (as 0.75 mg pramipexole dihydrochloride monohydrate).

Oprymea 1.05 mg prolonged-release tablets
Each prolonged-release tablet contains 1.05 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

Prolonged-release tablet

0.26 mg: White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P1 on one side, with bevelled edges and possible spots.
0.52 mg: White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P2 on one side, with bevelled edges and possible spots.
1.05 mg: White or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P3 on one side, with bevelled edges and possible spots.

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).

4.2 Posology and method of administration

Posology

Oprymea prolonged-release tablets are a once-a-day oral formulation of pramipexole.

Initial treatment
Doses should be increased gradually from a starting dose of 0.26 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 prolonged-release tablets		
Week	Daily dose (mg of base)	Daily dose (mg of salt)
1	0.26	0.375
2	0.52	0.75
3	1.05	1.5

If a further dose increase is necessary the daily dose should be increased by 0.52 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.15 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 1.05 mg of base (1.5 mg of salt) per day (see section 4.8).

Patients already taking Oprymea tablets may be switched to Oprymea prolonged-release tablets overnight, at the same daily dose. After switching to Oprymea prolonged-release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.26 mg of base (0.375 mg of salt) to a maximum of 3.15 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 1.05 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 1.05 mg of base (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.05 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).

Missed dose
When the intake of a dose is missed, Oprymea prolonged-release tablets should be taken within 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.

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 0.52 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.52 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.26 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 30 and 50 mL/min, treatment should be started with 0.26 mg Oprymea prolonged-release tablets every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week. If a further dose increase is necessary, doses should be increased by 0.26 mg pramipexole base at weekly intervals up to a maximum dose of 1.57 mg pramipexole base (2.25 mg of salt) per day.

The treatment of patients with a creatinine clearance below 30 mL/min with Oprymea prolonged-release tablets is not recommended as no data are available for this patient population. The use of Oprymea tablets should be considered.

If renal function declines during maintenance therapy, the recommendations given above should be followed.

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 prolonged-release tablets in the paediatric population for the indication of Parkinson's Disease.

Method of administration
The tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time.

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 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 Oprymea. 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. Co-administration 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.

Remnants in stool
Some patients have reported the occurrence of remnants in faeces which may resemble intact Oprymea prolonged-release tablets. If patients report such an observation, the physician should reassess patient's response to therapy.

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 1 778 Parkinson's disease patients on pramipexole and 1 297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% 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).

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.

Body System	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1000)**	**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 system disorders	somnolence dizziness dyskinesia	headache	sudden onset of 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		
Reproductive system and breast disorder				spontaneous penile erection	
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.

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 the national reporting system listed in Appendix V.

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.

Management
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 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.

Pharmacodynamic effects
In human volunteers, a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where pramipexole prolonged-release tablets were titrated faster (every 3 days) than recommended up to 3.15 mg pramipexole base (4.5 mg of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

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 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.

The safety and efficacy of pramipexole prolonged-release tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of three randomised, controlled trials. Two trials were conducted in patients with early Parkinson's disease and one trial was conducted in patients with advanced Parkinson's disease.

Superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (CGI-I and PGI-I responder rates) efficacy endpoints in a double-blind placebo-controlled trial including a total of 539 patients with early Parkinson's disease. Maintenance of efficacy was shown in patients treated for 33 weeks. Pramipexole prolonged-release tablets were non-inferior to pramipexole immediate release tablets as assessed on the UPDRS Parts II+III score at week 33.

In a double-blind placebo-controlled trial including a total of 517 patients with advanced Parkinson's disease who were on concomitant levodopa therapy superiority of pramipexole prolonged-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (off-time) efficacy endpoints.

The efficacy and tolerability of an overnight switch from pramipexole tablets to pramipexole prolonged-release tablets at the same daily dose were evaluated in a double-blind clinical study in patients with early Parkinson's disease.

Efficacy was maintained in 87 of 103 patients switched to pramipexole prolonged-release tablets. Out of these 87 patients, 82.8% did not change their dose, 13.8% increased and 3.4% decreased their dose. In half of the 16 patients who did not meet the criterion for maintained efficacy on UPDRS Part II+III score, the change from baseline was considered not clinically relevant.
Only one patient switched to pramipexole prolonged-release tablets experienced a drug-related adverse event leading to withdrawal.

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).

5.2 Pharmacokinetic properties

Absorption
Pramipexole is completely absorbed following oral administration. The absolute bioavailability is greater than 90%.

In a Phase I trial, where pramipexole immediate release and prolonged-release tablets were assessed in fasted state, the minimum and peak plasma concentration (C_{min}, C_{max}) and exposure (AUC) of the same daily dose of pramipexole prolonged-release tablets given once daily and pramipexole tablets given three times a day were equivalent.

The once daily administration of pramipexole prolonged-release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of pramipexole immediate release tablets.

The maximum plasma concentrations occur at about 6 hours after administration of pramipexole

prolonged-release tablets once daily. Steady state of exposure is reached at the latest after 5 days of continuous dosing.

Concomitant administration with food does generally not affect the bioavailability of pramipexole. Intake of a high fat meal induced an increase in peak concentration (C_{max}) of about 24% after a single dose administration and about 20% after multiple dose administrations and a delay of about 2 hours in time to reach peak concentration in healthy volunteers. Total exposure (AUC) was not affected by concomitant food intake. The increase in C_{max} is not considered clinically relevant. In the Phase III studies that established safety and efficacy of pramipexole prolonged-release tablets, patients were instructed to take study medication without regard to food intake.

While body weight has no impact on the AUC, it was found to influence the volume of distribution and therefore the peak concentrations C_{max}. A decreased body weight by 30 kg results in an increase in C_{max} of 45%. However, in Phase III trials in Parkinson's disease patients no clinically meaningful influence of body weight on the therapeutic effect and tolerability of pramipexole prolonged-release tablets was detected.

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 (t½) 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

Hypromellose
Maize starch
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 moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

3-week treatment initiation pack
Blister (OPA/Alu/desiccant/PE-Alu foil): 21 prolonged-release tablets (3 blisters of 7 tablets):
- 7 prolonged-release tablets of 0.26 mg
- 7 prolonged-release tablets of 0.52 mg
- 7 prolonged-release tablets of 1.05 mg

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)

21 prolonged-release tablets: EU/1/08/469/054

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

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.088 mg tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/001[20 tablets]
EU/1/08/469/002 [30 tablets]
EU/1/08/469/003 [60 tablets]
EU/1/08/469/004 [90 tablets]
EU/1/08/469/005 [100 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.088 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/(Alu/Alu)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.088 mg tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.18 mg tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/006 [20 tablets]
EU/1/08/469/007 [30 tablets]
EU/1/08/469/008 [60 tablets]
EU/1/08/469/009 [90 tablets]
EU/1/08/469/010 [100 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.18 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/(Alu/Alu)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.18 mg tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.35 mg tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/011 [20 tablets]
EU/1/08/469/012 [30 tablets]
EU/1/08/469/013 [60 tablets]
EU/1/08/469/014 [90 tablets]
EU/1/08/469/015 [100 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.35 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/(Alu/Alu)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.35 mg tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.7 mg tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/016 [20 tablets]
EU/1/08/469/017 [30 tablets]
EU/1/08/469/018 [60 tablets]
EU/1/08/469/019 [90 tablets]
EU/1/08/469/020 [100 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.7 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/(Alu/Alu)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.7 mg tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.1 mg tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/021 [20 tablets]
EU/1/08/469/022 [30 tablets]
EU/1/08/469/023 [60 tablets]
EU/1/08/469/024 [90 tablets]
EU/1/08/469/025 [100 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 1.1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/(Alu/Alu)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.1 mg tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 0.26 mg pramipexole (as 0.375 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/026 [10 prolonged-release tablets]
EU/1/08/469/027 [30 prolonged-release tablets]
EU/1/08/469/028 [90 prolonged-release tablets]
EU/1/08/469/029 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.26 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.52 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 0.52 mg pramipexole (as 0.75 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/030 [10 prolonged-release tablets]
EU/1/08/469/031[30 prolonged-release tablets]
EU/1/08/469/032[90 prolonged-release tablets]
EU/1/08/469/033[100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.52 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.52 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.05 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 1.05 mg pramipexole (as 1.5 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/034 [10 prolonged-release tablets]
EU/1/08/469/035 [30 prolonged-release tablets]
EU/1/08/469/036 [90 prolonged-release tablets]
EU/1/08/469/037 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 1.05 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.05 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.57 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 1.57 mg pramipexole (as 2.25 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/038 [10 prolonged-release tablets]
EU/1/08/469/039 [30 prolonged-release tablets]
EU/1/08/469/040 [90 prolonged-release tablets]
EU/1/08/469/041 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 1.57 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.57 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 2.1 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 2.1 mg pramipexole (as 3 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/042 [10 prolonged-release tablets]
EU/1/08/469/043 [30 prolonged-release tablets]
EU/1/08/469/044 [90 prolonged-release tablets]
EU/1/08/469/045 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 2.1 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 2.1 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 2.62 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 2.62 mg pramipexole (as 3.75 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/046 [10 prolonged-release tablets]
EU/1/08/469/047 [30 prolonged-release tablets]
EU/1/08/469/048 [90 prolonged-release tablets]
EU/1/08/469/049 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 2.62 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 2.62 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX for blisters

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 3.15 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 3.15 mg pramipexole (as 4.5 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

10 prolonged-release tablets
30 prolonged-release tablets
90 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/050 [10 prolonged-release tablets]
EU/1/08/469/051 [30 prolonged-release tablets]
EU/1/08/469/052 [90 prolonged-release tablets]
EU/1/08/469/053 [100 prolonged-release tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 3.15 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 3.15 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX (treatment initiation pack containing 3 boxes of 7 prolonged-release tablets)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg
Oprymea 0.52 mg
Oprymea 1.05 mg
prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Oprymea 0.26 mg: Each prolonged-release tablet contains 0.26 mg pramipexole (as 0.375 mg pramipexole dihydrochloride monohydrate).
Oprymea 0.52 mg: Each prolonged-release tablet contains 0.52 mg pramipexole (as 0.75 mg pramipexole dihydrochloride monohydrate).
Oprymea 1.05 mg: Each prolonged-release tablet contains 1.05 mg pramipexole (as 1.5 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

Treatment initiation pack
Each pack of 21 prolonged-release tablets for a 3-week treatment schedule contains:
7 tablets of Oprymea 0.26 mg
7 tablets of Oprymea 0.52 mg
7 tablets of Oprymea 1.05 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/054

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.26 mg
Oprymea 0.52 mg
Oprymea 1.05 mg
prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER BOX (week 1)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 0.26 mg pramipexole (as 0.375 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

7 prolonged-release tablets
Week 1

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/054

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.26 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister (week 1)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.26 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 1

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER BOX (week 2)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.52 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 0.52 mg pramipexole (as 0.75 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

7 prolonged-release tablets
Week 2

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/054

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 0.52 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister (week 2)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 0.52 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 2

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER BOX (week 3)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.05 mg prolonged-release tablets
pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 1.05 mg pramipexole (as 1.5 mg pramipexole dihydrochloride monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

7 prolonged-release tablets
Week 3

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Once daily.
Swallow whole, do not chew, divide or crush.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/469/054

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Oprymea 1.05 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister (week 3)

1. NAME OF THE MEDICINAL PRODUCT

Oprymea 1.05 mg prolonged-release tablets
pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 3

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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
pramipexole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Oprymea is and what it is used for
2. What you need to know before you take Oprymea
3. How to take Oprymea
4. Possible side effects
5. How to store Oprymea
6. Contents of the pack and other information

1. What Oprymea is and what it is used for

Oprymea contains the active substance pramipexole and belongs to a group of medicines known as dopamine agonists which stimulate dopamine receptors in the brain. Stimulation of the dopamine receptors triggers nerve impulses in the brain that help to control body movements.

Oprymea is used to:
- treat the symptoms of primary Parkinson's disease in adults. It can be used alone or in combination with levodopa (another medicine for Parkinson’s disease).
- treat the symptoms of moderate to severe primary Restless Legs Syndrome in adults.

2. What you need to know before you take Oprymea

Do not take Oprymea
- if you are allergic to pramipexole or to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking Oprymea. Tell your doctor if you have or have had or develop any medical conditions or symptoms, especially any of the following:
- Kidney disease
- Hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have advanced Parkinson’s disease and are also taking levodopa, you might develop dyskinesia during the up-titration of Oprymea
- Dystonia (inability of keeping your body and neck straight and upright (axial dystonia)). In particular, you may experience forward flexion of the head and neck (also called antecollis), forward bending of the lower back (also called camptocormia) or sidewards bending of the back

(also called pleurothotonus or Pisa Syndrome). If this happens, your doctor may want to change your medication.
- Sleepiness and episodes of suddenly falling asleep
- Psychosis (e.g. comparable with symptoms of schizophrenia)
- Vision impairment. You should have regular eye examinations during treatment with Oprymea
- Severe heart or blood vessels disease. You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up).
- Restless legs augmentation syndrome. If you experience that symptoms start earlier than usual in the evening (or even the afternoon), are more intense or involve larger parts of the affected limbs or involve other limbs. Your doctor may lower your dose or stop the treatment.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

Tell your doctor if you or your family/carer notices that you are developing mania (agitation, feeling elated or over-excited) or delirium (decreased awareness, confusion or loss of reality). Your doctor may need to adjust or stop your dose.

Tell your doctor if you experience symptoms such as depression, apathy, anxiety, fatigue, sweating or pain after stopping or reducing your Oprymea treatment. If the problems persist more than a few weeks, your doctor may need to adjust your treatment.

Children and adolescents
Oprymea is not recommended for use in children or adolescents under 18 years.

Other medicines and Oprymea
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You should avoid taking Oprymea together with antipsychotic medicines.

Take care if you are taking the following medicines:
- cimetidine (to treat excess stomach acid and stomach ulcers)
- amantadine (which can be used to treat Parkinson's disease)
- mexiletine (to treat irregular heartbeats, a condition known as ventricular arrhythmia)
- zidovudine (which can be used to treat the acquired immune deficiency syndrome (AIDS), a disease of the human immune system)
- cisplatin (to treat various types of cancers)
- quinine (which can be used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria (malignant malaria))
- procainamide (to treat irregular heart beat)

If you are taking levodopa, the dose of levodopa is recommended to be reduced when you start treatment with Oprymea.

Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol. In these cases Oprymea may affect your ability to drive and operate machinery.

Oprymea with food, drink and alcohol
You should be cautious while drinking alcohol during treatment with Oprymea.
Oprymea can be taken with or without food.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will then discuss with you if you should continue to take Oprymea.

The effect of Oprymea on the unborn child is not known. Therefore, do not take Oprymea if you are pregnant unless your doctor tells you to do so.

Oprymea should not be used during breast-feeding. Oprymea can reduce the production of breast milk. Also, it can pass into the breast milk and can reach your baby. If use of Oprymea is unavoidable, breast-feeding should be stopped.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Oprymea can cause hallucinations (seeing, hearing or feeling things that are not there). If affected, do not drive or use machines.
Oprymea has been associated with sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate machinery. Please tell your doctor if this occurs.

3. How to take Oprymea

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The doctor will advise you on the right dosing.

You can take Oprymea with or without food. Swallow the tablets with water.

Parkinson's disease
The daily dose is to be taken divided into 3 equal doses.

During the first week, the usual dose is 1 tablet Oprymea 0.088 mg three times a day (equivalent to 0.264 mg daily):

	1st week
Number of tablets	1 tablet Oprymea 0.088 mg three times a day
Total daily dose (mg)	0.264

This will be increased every 5 – 7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

	2nd week	**3rd week**
Number of tablets	1 tablet Oprymea 0.18 mg three times a day **OR** 2 tablets Oprymea 0.088 mg three times a day	1 tablet Oprymea 0.35 mg three times a day **OR** 2 tablets Oprymea 0.18 mg three times a day
Total daily dose (mg)	0.54	1.1

The usual maintenance dose is 1.1 mg per day. However, your dose may have to be increased even further. If necessary, your doctor may increase your tablet dose up to a maximum of 3.3 mg of pramipexole a day. A lower maintenance dose of three Oprymea 0.088 mg tablets a day is also possible.

	Lowest maintenance dose	**Highest maintenance dose**

Number of tablets	1 tablet Oprymea 0.088 mg three times a day	1 tablet Oprymea 1.1 mg three times a day
Total daily dose (mg)	0.264	3.3

Patients with kidney disease
If you have moderate or severe kidney disease, your doctor will prescribe a lower dose. In this case, you will have to take the tablets only once or twice a day. If you have moderate kidney disease, the usual starting dose is 1 tablet Oprymea 0.088 mg twice a day. In severe kidney disease, the usual starting dose is just 1 tablet Oprymea 0.088 mg a day.

Restless Legs Syndrome
The dose is usually taken once a day, in the evening, 2-3 hours before bedtime.

During the first week, the usual dose is 1 tablet Oprymea 0.088 mg once a day (equivalent to 0.088 mg daily):

	1st week
Number of tablets	1 tablet Oprymea 0.088 mg
Total daily dose (mg)	0.088

This will be increased every 4-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

	2nd week	3rd week	4th week
Number of tablets	1 tablet Oprymea 0.18 mg OR 2 tablets Oprymea 0.088 mg	1 tablet Oprymea 0.35 mg OR 2 tablets Oprymea 0.18 mg OR 4 tablets Oprymea 0.088 mg	1 tablet Oprymea 0.35 mg and 1 tablet Oprymea 0.18 mg OR 3 tablets Oprymea 0.18 mg OR 6 tablets Oprymea 0.088 mg
Total daily dose (mg)	0.18	0.35	0.54

The daily dose should not exceed 6 tablets Oprymea 0.088 mg or a dose of 0.54 mg (0.75 mg pramipexole salt).

If you stop taking your tablets for more than a few days and want to restart the treatment, you must start again at the lowest dose. You can then build up the dose again, as you did the first time. Ask your doctor for advice.

Your doctor will review your treatment after 3 months to decide whether or not to continue the treatment.

Patients with kidney disease
If you have severe kidney disease, Oprymea may not be a suitable treatment for you.

If you take more Oprymea than you should
If you accidentally take too many tablets:
- Contact your doctor or nearest hospital casualty department immediately for advice.
- You may experience vomiting, restlessness, or any of the side effects as described in section 4. "Possible side effects".

If you forget to take Oprymea
Do not worry. Simply leave out that dose completely and then take your next dose at the right time. Do not try to make up for the missed dose.

If you stop taking Oprymea
Do not stop taking Oprymea without first talking to your doctor. If you have to stop taking this medicine, your doctor will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson's disease you should not stop treatment with Oprymea abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:
- akinesia (loss of muscle movement)
- rigid muscles
- fever
- unstable blood pressure
- tachycardia (increased heart rate)
- confusion
- depressed level of consciousness (e.g. coma).

If you stop or reduce Oprymea you may also develop a medical condition called dopamine agonist withdrawal syndrome. The symptoms include depression, apathy, anxiety, fatigue, sweating or pain. If you experience these symptoms you should contact your physician.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Evaluation of these side effects is based on the following frequencies:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1 000 people
Very rare	may affect up to 1 in 10 000 people
Not known	frequency cannot be estimated from the available data

If you suffer from **Parkinson's disease**, you may experience the following side effects:

Very common:
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- Sleepiness
- Dizziness
- Nausea (sickness)

Common:
- Urge to behave in an unusual way
- Hallucinations (seeing, hearing or feeling things that are not there)
- Confusion
- Tiredness (fatigue)
- Sleeplessness (insomnia)
- Excess of fluid, usually in the legs (peripheral oedema)
- Headache
- Hypotension (low blood pressure)
- Abnormal dreams
- Constipation
- Visual impairment
- Vomiting (being sick)
- Weight loss including decreased appetite

Uncommon:
- Paranoia (e.g. excessive fear for one's own well-being)
- Delusion
- Excessive daytime sleepiness and suddenly falling asleep
- Amnesia (memory disturbance)
- Hyperkinesia (increased movements and inability to keep still)
- Weight increase
- Allergic reactions (e.g. rash, itching, hypersensitivity)
- Fainting
- Cardiac failure (heart problems which can cause shortness of breath or ankle swelling)*
- Inappropriate antidiuretic hormone secretion*
- Restlessness
- Dyspnoea (difficulties to breathe)
- Hiccups
- Pneumonia (infection of the lungs)
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
    - Strong impulse to gamble excessively despite serious personal or family consequences.
    - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.
    - Uncontrollable excessive shopping or spending
    - Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)*
- Delirium (decreased awareness, confusion, loss of reality)

Rare:
- Mania (agitation, feeling elated or over-excited)
- Spontaneous penile erection

Not known:
- After stopping or reducing your Oprymea treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (called dopamine agonist withdrawal syndrome or DAWS).

Tell your doctor if you experience any of these behaviours; he will discuss ways of managing or reducing the symptoms.

For the side effects marked with * a precise frequency estimation is not possible, since these side effects were not observed in clinical studies among 2 762 patients treated with pramipexole. The frequency category is probably not greater than "uncommon".

If you suffer from **Restless Legs Syndrome**, you may experience the following side effects:

Very common:
- Nausea (sickness).
- Symptoms that start earlier than usual, are more intense or involve other limbs (Restless legs augmentation syndrome).

Common:
- Changes in sleep pattern, such as sleeplessness (insomnia) and sleepiness
- Tiredness (fatigue)
- Headache
- Abnormal dreams
- Constipation
- Dizziness
- Vomiting (being sick)

Uncommon:
- Urge to behave in an unusual way*
- Cardiac failure (heart problems which can cause shortness of breath or ankle swelling)*
- Inappropriate antidiuretic hormone secretion*
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- Hyperkinesia (increased movements and inability to keep still)*
- Paranoia (e.g. excessive fear for one's own well-being)*
- Delusion*
- Amnesia (memory disturbance)*
- Hallucinations (seeing, hearing or feeling things that are not there)
- Confusion
- Excessive daytime sleepiness and suddenly falling asleep
- Weight increase
- Hypotension (low blood pressure)
- Excess of fluid, usually in the legs (peripheral oedema)
- Allergic reactions (e.g. rash, itching, hypersensitivity)
- Fainting
- Restlessness
- Visual impairment
- Weight loss including decreased appetite
- Dyspnoea (difficulties to breathe)
- Hiccups
- Pneumonia (infection of the lungs)*
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
    - Strong impulse to gamble excessively despite serious personal or family consequences.*
    - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.*
    - Uncontrollable excessive shopping or spending.*
    - Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)*
- Mania (agitation, feeling elated or over-excited)*
- Delirium (decreased awareness, confusion, loss of reality)*

Rare:
- Spontaneous penile erection

Not known:
- After stopping or reducing your Oprymea treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (called dopamine agonist withdrawal syndrome or DAWS).

Tell your doctor if you experience any of these behaviours; he will discuss ways of managing or reducing the symptoms.

For the side effects marked with * a precise frequency estimation is not possible, since these side effects were not observed in clinical studies among 1 395 patients treated with pramipexole. The frequency category is probably not greater than "uncommon".

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Oprymea

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Oprymea contains
- The active substance is pramipexole. Each tablet contains 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg or 1.1 mg pramipexole as 0.125 mg, 0.25 mg, 0.5 mg, 1 mg or 1.5 mg pramipexole dihydrochloride monohydrate, respectively.
- The other ingredients are mannitol, maize starch, pregelatinised maize starch, povidone K25, colloidal anhydrous silica and magnesium stearate.

What Oprymea looks like and contents of the pack
Oprymea 0.088 mg tablets are white, round, with bevelled edges and imprint "P6" on one side of the tablet.
Oprymea 0.18 mg tablets are 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 are 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 are 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 are white, round, with bevelled edges, both sides scored. The tablet can be divided into equal doses.

Boxes of 20, 30, 60, 90 and 100 tablets in blisters of 10 tablets are available.
Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Oprymea 0.26 mg prolonged-release tablets
Oprymea 0.52 mg prolonged-release tablets
Oprymea 1.05 mg prolonged-release tablets
Oprymea 1.57 mg prolonged-release tablets
Oprymea 2.1 mg prolonged-release tablets
Oprymea 2.62 mg prolonged-release tablets
Oprymea 3.15 mg prolonged-release tablets
pramipexole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Oprymea is and what it is used for
2. What you need to know before you take Oprymea
3. How to take Oprymea
4. Possible side effects
5. How to store Oprymea
6. Contents of the pack and other information

1. What Oprymea is and what it is used for

Oprymea contains the active substance pramipexole and belongs to a group of medicines known as dopamine agonists, which stimulate dopamine receptors in the brain. Stimulation of the dopamine receptors triggers nerve impulses in the brain that help to control body movements.

Oprymea is used to treat the symptoms of primary Parkinson's disease in adults. It can be used alone or in combination with levodopa (another medicine for Parkinson's disease).

2. What you need to know before you take Oprymea

Do not take Oprymea
- if you are allergic to pramipexole or to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking Oprymea. Tell your doctor if you have (had) or develop any medical conditions or symptoms, especially any of the following:
- Kidney disease
- Hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have advanced Parkinson's disease and are also taking levodopa, you might develop dyskinesia during the up-titration of Oprymea
- Dystonia (inability of keeping your body and neck straight and upright (axial dystonia)). In particular, you may experience forward flexion of the head and neck (also called antecollis), forward bending of the lower back (also called camptocormia) or sidewards bending of the back

(also called pleurothotonus or Pisa Syndrome). If this happens, your doctor may want to change your medication.
- Sleepiness and episodes of suddenly falling asleep
- Psychosis (e.g. comparable with symptoms of schizophrenia)
- Vision impairment. You should have regular eye examinations during treatment with Oprymea
- Severe heart or blood vessels disease. You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up).

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

Tell your doctor if you or your family/carer notices that you are developing mania (agitation, feeling elated or over-excited) or delirium (decreased awareness, confusion or loss of reality). Your doctor may need to adjust or stop your dose.

Tell your doctor if you experience symptoms such as depression, apathy, anxiety, fatigue, sweating or pain after stopping or reducing your Oprymea treatment. If the problems persist more than a few weeks, your doctor may need to adjust your treatment.

Oprymea prolonged-release tablet is a specially designed tablet from which the active ingredient is gradually released, once the tablet has been ingested. Parts of tablets may occasionally be passed and seen in the stool (faeces) and may look like whole tablets. Inform your doctor if you find tablet pieces in your faeces.

Children and adolescents
Oprymea is not recommended for use in children or adolescents under 18 years.

Other medicines and Oprymea
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You should avoid taking Oprymea together with antipsychotic medicines.

Take care if you are taking the following medicines:
- cimetidine (to treat excess stomach acid and stomach ulcers)
- amantadine (which can be used to treat Parkinson's disease)
- mexiletine (to treat irregular heartbeats, a condition known as ventricular arrhythmia)
- zidovudine (which can be used to treat the acquired immune deficiency syndrome (AIDS), a disease of the human immune system)
- cisplatin (to treat various types of cancers)
- quinine (which can be used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria (malignant malaria))
- procainamide (to treat irregular heart beat).

If you are taking levodopa, the dose of levodopa is recommended to be reduced when you start treatment with Oprymea.

Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol. In these cases Oprymea may affect your ability to drive and operate machinery.

Oprymea with food, drink and alcohol

You should be cautious while drinking alcohol during treatment with Oprymea.
Oprymea can be taken with or without food.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will then discuss with you if you should continue to take Oprymea.

The effect of Oprymea on the unborn child is not known. Therefore, do not take Oprymea if you are pregnant unless your doctor tells you to do so.

Oprymea should not be used during breast-feeding. Oprymea can reduce the production of breast milk. Also, it can pass into the breast milk and can reach your baby. If use of Oprymea is unavoidable, breast-feeding should be stopped.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Oprymea can cause hallucinations (seeing, hearing or feeling things that are not there). If affected, do not drive or use machines.

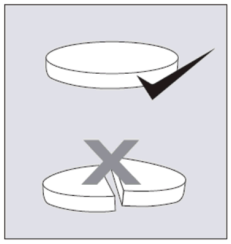
Oprymea has been associated with sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate machinery. You should tell your doctor if this occurs.

3. How to take Oprymea

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The doctor will advise you on the right dosing.

Take Oprymea prolonged-release tablets only once a day and each day at about the same time.

You can take Oprymea with or without food. Swallow the tablets whole with water.



Do not chew, divide or crush the prolonged-release tablets. If you do, there is a danger you could overdose, because the medicine may be released into your body too quickly.

During the first week, the usual daily dose is 0.26 mg pramipexole. The dose will be increased every 5-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

Ascending dose schedule of Oprymea prolonged-release tablets		
Week	Daily dose (mg)	Number of tablets
1	0.26	One Oprymea 0.26 mg prolonged-release tablet.
2	0.52	One Oprymea 0.52 mg prolonged-release tablet, OR two Oprymea 0.26 mg prolonged-release tablets.
3	1.05	One Oprymea 1.05 mg prolonged-release tablet, OR two Oprymea 0.52 mg prolonged-release tablets, OR four Oprymea 0.26 mg prolonged-release tablets.

The usual maintenance dose is 1.05 mg per day. However, your dose may have to be increased even further. If necessary, your doctor may increase your dose up to a maximum of 3.15 mg of pramipexole a day. A lower maintenance dose of one Oprymea 0.26 mg prolonged-release tablet a day is also possible.

Patients with kidney disease
If you have kidney disease, your doctor may advise you to take the usual starting dose of 0.26 mg prolonged-release tablets only every other day for the first week. After that, your doctor may increase the dosing frequency to one 0.26 mg prolonged-release tablet every day. If a further dose increase is necessary, your doctor may adjust it in steps of 0.26 mg pramipexole.

If you have serious kidney problems, your doctor may need to switch you to a different pramipexole medicine. If during treatment your kidney problems get worse, you should contact your doctor as soon as possible.

If you are switching from Oprymea (immediate release) tablets
Your doctor will base your dose of Oprymea prolonged-release tablets on the dose of Oprymea (immediate release) tablets you were taking.

Take your Oprymea (immediate release) tablets as normal the day before you switch. Then take your Oprymea prolonged-release tablets next morning and do not take any more Oprymea (immediate release) tablets.

If you take more Oprymea than you should
If you accidentally take too many tablets,
- Contact your doctor or nearest hospital casualty department immediately for advice.
- You may experience vomiting, restlessness, or any of the side effects as described in chapter 4 "Possible side effects".

If you forget to take Oprymea
If you forget to take a dose of Oprymea, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time.
If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet dose.

If you stop taking Oprymea
Do not stop taking Oprymea without first talking to your doctor. If you have to stop taking this medicine, your doctor will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson’s disease you should not stop treatment with Oprymea abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:
- akinesia (loss of muscle movement)
- rigid muscles
- fever
- unstable blood pressure
- tachycardia (increased heart rate)
- confusion
- depressed level of consciousness (e.g. coma).

If you stop or reduce Oprymea you may also develop a medical condition called dopamine agonist withdrawal syndrome. The symptoms include depression, apathy, anxiety, fatigue, sweating or pain. If you experience these symptoms you should contact your physician.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Evaluation of these side effects is based on the following frequencies:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1 000 people
Very rare	may affect up to 1 in 10 000 people
Not known	frequency cannot be estimated from the available data

You may experience the following side effects:

Very common:
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- Sleepiness
- Dizziness
- Nausea (sickness)

Common:
- Urge to behave in an unusual way
- Hallucinations (seeing, hearing or feeling things that are not there)
- Confusion
- Tiredness (fatigue)
- Sleeplessness (insomnia)
- Excess of fluid, usually in the legs (peripheral oedema)
- Headache
- Hypotension (low blood pressure)
- Abnormal dreams
- Constipation
- Visual impairment
- Vomiting (being sick)
- Weight loss including decreased appetite

Uncommon:
- Paranoia (e.g. excessive fear for one's own well-being)
- Delusion
- Excessive daytime sleepiness and suddenly falling asleep
- Amnesia (memory disturbance)
- Hyperkinesia (increased movements and inability to keep still)
- Weight increase
- Allergic reactions (e.g. rash, itching, hypersensitivity)
- Fainting
- Cardiac failure (heart problems which can cause shortness of breath or ankle swelling)*
- Inappropriate antidiuretic hormone secretion*
- Restlessness
- Dyspnoea (difficulties to breathe)
- Hiccups
- Pneumonia (infection of the lungs)
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - Strong impulse to gamble excessively despite serious personal or family consequences.
  - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.

- Uncontrollable excessive shopping or spending
- Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)*

- Delirium (decreased awareness, confusion, loss of reality)

Rare:
- Mania (agitation, feeling elated or over-excited)
- Spontaneous penile erection

Not known:
- After stopping or reducing your Oprymea treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (called dopamine agonist withdrawal syndrome or DAWS).

Tell your doctor if you experience any of these behaviours; he will discuss ways of managing or reducing the symptoms.

For the side effects marked with * a precise frequency estimation is not possible, since these side effects were not observed in clinical studies among 2 762 patients treated with pramipexole. The frequency category is probably not greater than "uncommon".

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Oprymea

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.
This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Oprymea contains
- The active substance is pramipexole. Each prolonged-release tablet contains 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg or 3.15 mg pramipexole as 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg or 4.5 mg pramipexole dihydrochloride monohydrate, respectively.
- The other ingredients are hypromellose, maize starch, colloidal anhydrous silica and magnesium stearate.

What Oprymea looks like and contents of the pack
Oprymea 0.26 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P1 on one side, with bevelled edges and possible spots.
Oprymea 0.52 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P2 on one side, with bevelled edges and possible spots.
Oprymea 1.05 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P3 on one side, with bevelled edges and possible spots.

Oprymea 1.57 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P12 on one side, with bevelled edges and possible spots.
Oprymea 2.1 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P4 on one side, with bevelled edges and possible spots.
Oprymea 2.62 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P13 on one side and 262 on the other side, with bevelled edges and possible spots.
Oprymea 3.15 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P5 on one side and 315 on the other side, with bevelled edges and possible spots.

Boxes of 10, 30, 90 and 100 tablets in blisters of 10 tablets are available.
Not all pack sizes may be marketed.

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Package leaflet: Information for the patient

Oprymea 0.26 mg prolonged-release tablets
Oprymea 0.52 mg prolonged-release tablets
Oprymea 1.05 mg prolonged-release tablets
pramipexole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
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What is in this leaflet

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2. What you need to know before you take Oprymea
3. How to take Oprymea
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1. What Oprymea is and what it is used for

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Oprymea is used to treat the symptoms of primary Parkinson's disease in adults. It can be used alone or in combination with levodopa (another medicine for Parkinson's disease).

2. What you need to know before you take Oprymea

Do not take Oprymea
- if you are allergic to pramipexole or to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking Oprymea. Tell your doctor if you have (had) or develop any medical conditions or symptoms, especially any of the following:
- Kidney disease
- Hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have advanced Parkinson's disease and are also taking levodopa, you might develop dyskinesia during the up-titration of Oprymea
- Dystonia (inability of keeping your body and neck straight and upright (axial dystonia)). In particular, you may experience forward flexion of the head and neck (also called antecollis), forward bending of the lower back (also called camptocormia) or sidewards bending of the back (also called pleurothotonus or Pisa Syndrome). If this happens, your doctor may want to change your medication.
- Sleepiness and episodes of suddenly falling asleep
- Psychosis (e.g. comparable with symptoms of schizophrenia)

- Vision impairment. You should have regular eye examinations during treatment with Oprymea
- Severe heart or blood vessels disease. You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up).

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

Tell your doctor if you or your family/carer notices that you are developing mania (agitation, feeling elated or over-excited) or delirium (decreased awareness, confusion or loss of reality). Your doctor may need to adjust or stop your dose.

Tell your doctor if you experience symptoms such as depression, apathy, anxiety, fatigue, sweating or pain after stopping or reducing your Oprymea treatment. If the problems persist more than a few weeks, your doctor may need to adjust your treatment.

Oprymea prolonged-release tablet is a specially designed tablet from which the active ingredient is gradually released, once the tablet has been ingested. Parts of tablets may occasionally be passed and seen in the stool (faeces) and may look like whole tablets. Inform your doctor if you find tablet pieces in your faeces.

Children and adolescents
Oprymea is not recommended for use in children or adolescents under 18 years.

Other medicines and Oprymea
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

You should avoid taking Oprymea together with antipsychotic medicines.

Take care if you are taking the following medicines:
- cimetidine (to treat excess stomach acid and stomach ulcers);
- amantadine (which can be used to treat Parkinson's disease);
- mexiletine (to treat irregular heartbeats, a condition known as ventricular arrhythmia);
- zidovudine (which can be used to treat the acquired immune deficiency syndrome (AIDS), a disease of the human immune system);
- cisplatin (to treat various types of cancers);
- quinine (which can be used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria (malignant malaria));
- procainamide (to treat irregular heart beat).

If you are taking levodopa, the dose of levodopa is recommended to be reduced when you start treatment with Oprymea.

Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol. In these cases Oprymea may affect your ability to drive and operate machinery.

Oprymea with food, drink and alcohol
You should be cautious while drinking alcohol during treatment with Oprymea.
Oprymea can be taken with or without food.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will then discuss with you if you should continue to take Oprymea.

The effect of Oprymea on the unborn child is not known. Therefore, do not take Oprymea if you are pregnant unless your doctor tells you to do so.

Oprymea should not be used during breast-feeding. Oprymea can reduce the production of breast milk. Also, it can pass into the breast milk and can reach your baby. If use of Oprymea is unavoidable, breast-feeding should be stopped.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Oprymea can cause hallucinations (seeing, hearing or feeling things that are not there). If affected, do not drive or use machines.

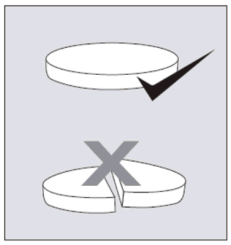
Oprymea has been associated with sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate machinery. You should tell your doctor if this occurs.

3. How to take Oprymea

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The doctor will advise you on the right dosing.

Take Oprymea prolonged-release tablets only once a day and each day at about the same time.

You can take Oprymea with or without food. Swallow the tablets whole with water.



Do not chew, divide or crush the prolonged-release tablets. If you do, there is a danger you could overdose, because the medicine may be released into your body too quickly.

During the first week, the usual daily dose is 0.26 mg pramipexole. The dose will be increased every 5-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

The Oprymea treatment initiation pack is only to be used for the beginning of the treatment with Oprymea.
The Oprymea treatment initiation pack contains three blister strips of tablets - one strip for each of the first three weeks of your treatment. The three strips are marked with "Week 1", "Week 2" and "Week 3".
The daily dose you take of Oprymea increases each week.

Ascending dose schedule of Oprymea prolonged-release tablets		
Week	Daily dose (mg)	Number of tablets
1	0.26	One Oprymea 0.26 mg prolonged-release tablet on blister "Week 1".
2	0.52	One Oprymea 0.52 mg prolonged-release tablet on blister "Week 2".
3	1.05	One Oprymea 1.05 mg prolonged-release tablet on blister "Week 3".

The usual maintenance dose is 1.05 mg per day. However, your dose may have to be increased even further. If necessary, your doctor may increase your dose up to a maximum of 3.15 mg of pramipexole

a day. A lower maintenance dose of one Oprymea 0.26 mg prolonged-release tablet a day is also possible.

Patients with kidney disease
If you have kidney disease, your doctor may advise you to take the usual starting dose of 0.26 mg prolonged-release tablets only every other day for the first week. After that, your doctor may increase the dosing frequency to one 0.26 mg prolonged-release tablet every day. If a further dose increase is necessary, your doctor may adjust it in steps of 0.26 mg pramipexole.

If you have serious kidney problems, your doctor may need to switch you to a different pramipexole medicine. If during treatment your kidney problems get worse, you should contact your doctor as soon as possible.

If you are switching from Oprymea (immediate release) tablets
Your doctor will base your dose of Oprymea prolonged-release tablets on the dose of Oprymea (immediate release) tablets you were taking.

Take your Oprymea (immediate release) tablets as normal the day before you switch. Then take your Oprymea prolonged-release tablets next morning and do not take any more Oprymea (immediate release) tablets.

If you take more Oprymea than you should
If you accidentally take too many tablets,
- Contact your doctor or nearest hospital casualty department immediately for advice.
- You may experience vomiting, restlessness, or any of the side effects as described in chapter 4 "Possible side effects".

If you forget to take Oprymea
If you forget to take a dose of Oprymea, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time.
If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet dose.

If you stop taking Oprymea
Do not stop taking Oprymea without first talking to your doctor. If you have to stop taking this medicine, your doctor will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson's disease you should not stop treatment with Oprymea abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:
- akinesia (loss of muscle movement)
- rigid muscles
- fever
- unstable blood pressure
- tachycardia (increased heart rate)
- confusion
- depressed level of consciousness (e.g. coma).

If you stop or reduce Oprymea you may also develop a medical condition called dopamine agonist withdrawal syndrome. The symptoms include depression, apathy, anxiety, fatigue, sweating or pain. If you experience these symptoms you should contact your physician.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Evaluation of these side effects is based on the following frequencies:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1 000 people
Very rare	may affect up to 1 in 10 000 people
Not known	frequency cannot be estimated from the available data

You may experience the following side effects:

Very common:
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- Sleepiness
- Dizziness
- Nausea (sickness)

Common:
- Urge to behave in an unusual way
- Hallucinations (seeing, hearing or feeling things that are not there)
- Confusion
- Tiredness (fatigue)
- Sleeplessness (insomnia)
- Excess of fluid, usually in the legs (peripheral oedema)
- Headache
- Hypotension (low blood pressure)
- Abnormal dreams
- Constipation
- Visual impairment
- Vomiting (being sick)
- Weight loss including decreased appetite

Uncommon:
- Paranoia (e.g. excessive fear for one's own well-being)
- Delusion
- Excessive daytime sleepiness and suddenly falling asleep
- Amnesia (memory disturbance)
- Hyperkinesia (increased movements and inability to keep still)
- Weight increase
- Allergic reactions (e.g. rash, itching, hypersensitivity)
- Fainting
- Cardiac failure (heart problems which can cause shortness of breath or ankle swelling)*
- Inappropriate antidiuretic hormone secretion*
- Restlessness
- Dyspnoea (difficulties to breathe)
- Hiccups
- Pneumonia (infection of the lungs)
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
    - Strong impulse to gamble excessively despite serious personal or family consequences.
    - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.
    - Uncontrollable excessive shopping or spending
    - Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)*

- Delirium (decreased awareness, confusion, loss of reality)

Rare:
- Mania (agitation, feeling elated or over-excited)
- Spontaneous penile erection

Not known:
- After stopping or reducing your Oprymea treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (called dopamine agonist withdrawal syndrome or DAWS).

Tell your doctor if you experience any of these behaviours; he will discuss ways of managing or reducing the symptoms.

For the side effects marked with * a precise frequency estimation is not possible, since these side effects were not observed in clinical studies among 2 762 patients treated with pramipexole. The frequency category is probably not greater than "uncommon".

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Oprymea

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.
This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Oprymea contains
- The active substance is pramipexole. Each prolonged-release tablet contains 0.26 mg, 0.52 mg or 1.05 mg pramipexole as 0.375 mg, 0.75 mg or 1.5 mg pramipexole dihydrochloride monohydrate, respectively.
- The other ingredients are hypromellose, maize starch, colloidal anhydrous silica and magnesium stearate.

What Oprymea looks like and contents of the pack
Oprymea 0.26 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P1 on one side, with bevelled edges and possible spots.
Oprymea 0.52 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P2 on one side, with bevelled edges and possible spots.
Oprymea 1.05 mg prolonged-release tablets are white or almost white, round (diameter 10 mm), slightly biconvex tablets engraved with P3 on one side, with bevelled edges and possible spots.

3-week treatment initiation pack contains 21 prolonged-release tablets in 3 packages:
- the package marked "Week 1" contains 1 blister of 7 tablets of 0.26 mg,

- the package marked "Week 2" contains 1 blister of 7 tablets of 0.52 mg,
- the package marked "Week 3" contains 1 blister of 7 tablets of 1.05 mg.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.