ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 0.088 mg tablets
Pramipexole Accord 0.18 mg tablets
Pramipexole Accord 0.35 mg tablets
Pramipexole Accord 0.7 mg tablets
Pramipexole Accord 1.1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pramipexole Accord 0.088 mg tablet
Each tablet contains 0.125 mg pramipexole dihydrochloride monohydrate equivalent to 0.088 mg pramipexole.

Pramipexole Accord 0.18 mg tablet
Each tablet contains 0.25 mg pramipexole dihydrochloride monohydrate equivalent to 0.18 mg pramipexole.

Pramipexole Accord 0.35 mg tablet
Each tablet contains 0.5 mg pramipexole dihydrochloride monohydrate equivalent to 0.35 mg pramipexole.

Pramipexole Accord 0.7 mg tablet
Each tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.

Pramipexole Accord 1.1 mg tablet
Each tablet contains 1.5 mg pramipexole dihydrochloride monohydrate equivalent to 1.1 mg pramipexole.

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.

Pramipexole Accord 0.088 mg tablet
The tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I1’ on one side and plain on the other side.

Pramipexole Accord 0.18 mg tablet
The tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I’ and ‘2’ on either side of the breakline on one side and breakline on the other side.

The tablet can be divided into two equal doses.

Pramipexole Accord 0.35 mg tablet
The tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I’ and ‘3’ on either side of the breakline on one side and breakline on the other side.

The tablet can be divided into two equal doses.

Pramipexole Accord 0.7 mg tablet
The tablets are white to off-white, round, flat faced, bevel edged, with inscription 'I' and '4' on either side of the breakline on one side and breakline on the other side.

The tablet can be divided into two equal doses.

Pramipexole Accord 1.1 mg tablet
The tablets are white to off-white, round, flat faced, bevel edged, with inscription 'I' and '5' on either side of the breakline on one side and breakline on other side.

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pramipexole Accord 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

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

If a further dose increase is necessary the daily dose should be increased by 0.54 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg (of salt) per day (see section 4.8).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In

clinical trials approximately 5% of patients were treated at doses below 1.1 mg of base (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.1 mg of base (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole Accord, 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. 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).

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 Pramipexole Accord 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 Pramipexole Accord 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 Pramipexole Accord 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 Pramipexole Accord 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 Pramipexole Accord pharmacokinetics has not been investigated.

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

Tourette Disorder

Paediatric population
Pramipexole Accord is not recommended for use in children and adolescents below 18 years since the efficacy and safety has not been established in this population. Pramipexole Accord 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 Pramipexole Accord 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 Pramipexole Accord. 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 Pramipexole Accord. 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 Accord. 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
To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off (see section 4.2). Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain which may be severe. Patients should be informed about this before tapering the dopamine agonist, and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the pramipexole dose temporarily (see section 4.8).

Augmentation

Reports in the literature indicate that treatment of another indication with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Augmentation was observed in 11.8% of patients in the pramipexole group (N = 152) and 9.4% of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between pramipexole and placebo groups.

4.5 Interaction with other medicinal products and other forms of interaction

Plasma protein binding

Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway

Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, and procainamide, may

interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole Accord.

Combination with levodopa

When Pramipexole Accord 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 Pramipexole Accord.

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). Pramipexole Accord should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

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, Pramipexole Accord 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

Pramipexole Accord has major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole Accord 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		
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.

Other indication, most common adverse reactions

The most commonly (≥ 5%) reported adverse drug reactions in patients with other indication treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with Pramipexole Accord (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).

Table 2: Other indication

Body System	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Not known**
Infections and infestations			pneumonia[1]	
Endocrine disorders			inappropriate antidiuretic hormone secretion[1]	
Psychiatric disorders		insomnia abnormal dreams	restlessness confusion hallucinations libido disorder delusion[1] hyperphagia[1] paranoia[1] mania[1] delirium[1]	

			behavioural symptoms of impulse control disorders and compulsions[1] (such as: compulsive shopping, pathological gambling, hypersexuality, binge eating)	
Nervous system disorders		headache dizziness somnolance	sudden onset of sleep syncope dyskinesia amnesia[1] hyperkinesia[1]	
Eye disorders			visual impairment including visual acuity reduced diplopia vision blurred	
Cardiac disorders			cardiac failure[1]	
Vascular disorders			hypotension	
Respiratory, thoracic, and mediastinal disorders			dyspnoea hiccups	
Gastrointestinal disorders	nausea	constipation vomiting		
Skin and subcutaneous tissue disorders			hypersensitivity pruritus rash	
General disorders and 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 other indication 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 Pramipexole Accord. (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 ($\leq$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 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 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.

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 Accord 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 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 14C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400 ml/min. The elimination half-life (t½) varies from 8 hours in the young to 12 hours in the elderly.

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
Cellulose, microcrystalline
Maize starch
Silica, colloidal anhydrous
Povidone

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Pramipexole Accord tablets are packed in alu-alu blisters.

Each blister strip contains 10 tablets.
Pack-sizes of 30 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

Pramipexole Accord 0.088 mg tablet
EU/1/11/728/001-002 (30/100 tablets in alu/alu blister)

Pramipexole Accord 0.18 mg tablet
EU/1/11/728/003-004 (30/100 tablets in alu/alu blister)

Pramipexole Accord 0.35 mg tablet
EU/1/11/728/005-006 (30/100 tablets in alu/alu blister)

Pramipexole Accord 0.7 mg tablet
EU/1/11/728/007-008 (30/100 tablets in alu/alu blister)

Pramipexole Accord 1.1 mg tablet
EU/1/11/728/009-010 (30/100 tablets in alu/alu blister)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 September 2011
Date of latest renewal: 15th July 2016

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. CONSITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDISTIONS 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 manufacturer responsible for batch release

Accord Healthcare Ltd.
Sage House
319 Pinner road
North Harrow, Middx HA1 4HF
United Kingdom

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

Accord Healthcare B.V.,
Winthontlaan 200,
3526 KV Utrecht,
The Netherlands

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**

The requirements for submission of periodic safety update reports 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 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

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 0.088 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.125 mg pramipexole dihydrochloride monohydrate equivalent to 0.088 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION:

Read the package leaflet before use.
For 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 below 30°C. 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

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/728/001-002 (30/100 tablets in alu/alu blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Accord 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

Pramipexole Accord 0.088 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 0.18 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.25 mg pramipexole dihydrochloride monohydrate equivalent to 0.18 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION:

Read the package leaflet before use.
For 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 below 30°C. 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

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/728/003-004 (30/100 tablets in alu/alu blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Accord 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

Pramipexole Accord 0.18 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 0.35 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg pramipexole dihydrochloride monohydrate equivalent to 0.35 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION:

Read the package leaflet before use.
For 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 below 30°C. 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

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/728/005-006 (30/100 tablets in alu/alu blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Accord 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

Pramipexole Accord 0.35 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 0.7 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION:

Read the package leaflet before use.
For 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 below 30°C. 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

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/728/007-008 (30/100 tablets in alu/alu blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Accord 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

Pramipexole Accord 0.7 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for blisters

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Accord 1.1 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1.5 mg pramipexole dihydrochloride monohydrate equivalent to 1.1 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION:

Read the package leaflet before use.
For 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 below 30°C. 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

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/728/009-010 (30/100 tablets in alu/alu blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Accord 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

Pramipexole Accord 1.1 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pramipexole Accord 0.088 mg tablets
Pramipexole Accord 0.18 mg tablets
Pramipexole Accord 0.35 mg tablets
Pramipexole Accord 0.7 mg tablets
Pramipexole Accord 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 of the 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 Pramipexole Accord is and what it is used for

Pramipexole Accord 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.

Pramipexole Accord 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 Pramipexole Accord

Do not take Pramipexole Accord:
- 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 Pramipexole Accord. 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 Pramipexole Accord.
- 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 Pramipexole Accord.
- 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).
- Augmentation. You may experience that symptoms start earlier than usual, be more intense and involve other limbs.

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 Pramipexole Accord treatment. If the problems persist more than a few weeks, your doctor may need to adjust your treatment.

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

Other medicines and Pramipexole Accord
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 Pramipexole Accord 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 Pramipexole Accord.

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 Pramipexole Accord may affect your ability to drive and operate machinery.

Pramipexole Accord with food, drink and alcohol
You should be cautious while drinking alcohol during treatment with Pramipexole Accord. Pramipexole Accord 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 for advice before taking this medicine. Your doctor will then discuss with you if you should continue to take Pramipexole Accord.

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

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

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

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

Pramipexole Accord 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 Pramipexole Accord

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

You can take Pramipexole Accord 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 Pramipexole Accord 0.088 mg three times a day (equivalent to 0.264 mg daily):

	1st week
Number of tablets	1 Pramipexole Accord tablet 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 Pramipexole Accord tablet 0.18 mg three times a day OR 2 Pramipexole Accord tablets 0.088 mg three times a day	1 Pramipexole Accord tablet 0.35 mg three times a day OR 2 Pramipexole Accord tablets 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 Pramipexole Accord 0.088 mg tablets a day is also possible.

	Lowest maintenance dose	Highest maintenance dose
Number of tablets	1 Pramipexole Accord tablet 0.088 mg three times a day	1 Pramipexole Accord tablet 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 Pramipexole Accord tablet 0.088 mg twice a day. In severe kidney disease, the usual starting dose is just 1 Pramipexole Accord tablet 0.088 mg a day.

If you take more Pramipexole Accord 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 Pramipexole Accord
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 Pramipexole Accord
Do not stop taking Pramipexole Accord 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 Pramipexole Accord 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 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)

Not known:
- After stopping or reducing your Pramipexole Accord 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 other indication, you may experience the following side effects:

Very common:
- Nausea (sickness)

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)*

Not known:
- After stopping or reducing your Pramipexole Accord 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 behaviors; 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, pharmacist or nurse. 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 Pramipexole Accord

- 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 carton after EXP. The expiry date refers to the last day of that month.
- Store below 30°C. 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 to protect the environment.

6. Contents of the pack and other information

What Pramipexole Accord tablet contains:

The active ingredient is pramipexole.

Each tablet contains 0.125 mg pramipexole dihydrochloride monohydrate equivalent to 0.088 mg pramipexole.
Each tablet contains 0.25 mg pramipexole dihydrochloride monohydrate equivalent to 0.18 mg pramipexole.
Each tablet contains 0.5 mg pramipexole dihydrochloride monohydrate equivalent to 0.35 mg pramipexole.
Each tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.
Each tablet contains 1.5 mg pramipexole dihydrochloride monohydrate equivalent to 1.1 mg pramipexole.

The other ingredients are mannitol, cellulose microcrystalline, maize starch, silica colloidal anhydrous, povidone K 30 and magnesium stearate.

What Pramipexole Accord tablet looks like and contents of the pack

Pramipexole Accord 0.088 mg tablets are white to off-white, round, flat faced, bevel edged, with inscription 'I1' on one side and plain on the other side.

Pramipexole Accord 0.18 mg tablets are white to off-white, round, flat faced, bevel edged, with inscription 'I' and '2' on either side of the breakline on one side and breakline on the other side.

Pramipexole Accord 0.35 mg tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I’ and ‘3’ on either side of the breakline on one side and breakline on the other side.

Pramipexole Accord 0.7 mg tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I’ and ‘4’ on either side of the breakline on one side and breakline on the other side..

Pramipexole Accord 1.1 mg tablets are white to off-white, round, flat faced, bevel edged, with inscription ‘I’ and ‘5’ on either side of the breakline on one side and breakline on other side.

All the strengths of Pramipexole Accord tablets are available in alu-alu blisters of 10 tablets per strip, in cartons containing 3 or 10 blister strips (30 or 100 tablets).
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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