ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.088 mg tablets
Pramipexole Teva 0.18 mg tablets
Pramipexole Teva 0.35 mg tablets
Pramipexole Teva 0.7 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Pramipexole Teva 0.7 mg tablets
Each tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 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 Teva 0.088 mg tablets
White, round, flat face bevel edge tablet, 5.55 mm diameter, embossed with “93” on one side and “P1” on the other side.

Pramipexole Teva 0.18 mg tablets
White, round, flat face bevel edge tablet, 7.00 mm diameter, embossed with "P2" over "P2" on the scored side and "93" on the other side. The tablet can be divided into equal halves.

Pramipexole Teva 0.35 mg tablets
White to off-white, oval, biconvex tablets, engraved with 9 vertical scoreline 3 on the scored side, and 8023 on the other side. The tablet can be divided into equal halves.

Pramipexole Teva 0.7 mg tablets
White, round, flat face bevel edge tablet, 8.82 mm diameter, embossed with "8024" over "8024" on the scored side and "93" on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pramipexole Teva 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 Teva				
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 Teva, 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 Teva 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 Teva 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 Teva 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 Teva 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 Teva pharmacokinetics has not been investigated.

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

Tourette Disorder

Paediatric population
Pramipexole Teva 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 Teva 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 Teva 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 Teva. 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 Teva. 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 Teva. 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 Teva.

Combination with levodopa
When Pramipexole Teva 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 Teva.

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 Teva 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, Pramipexole Teva 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 Teva can have a major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole Teva 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 another indication treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with pramipexole (20.8 % and 10.5 %, respectively) compared to males (6.7 % and 7.3 %, respectively).

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 somnolence	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 when 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 Teva (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 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.

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.

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 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
Microcrystalline cellulose
Sodium starch glycolate
Povidone K25
Magnesium stearate
Sodium stearyl fumarate
Colloidal silicon dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium/Aluminium Blister
Pack sizes: 30, 30 x 1, 50 x 1, 100 x 1 and 100 tablets

Polyethylene tablet container with CRC polypropylene cap. Pack sizes: 90 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5, 2031GA Haarlem

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Pramipexole Teva 0.088 mg tablets
EU/1/08/490/001
EU/1/08/490/002
EU/1/08/490/003
EU/1/08/490/004
EU/1/08/490/017
EU/1/08/490/018

Pramipexole Teva 0.18 mg tablets
EU/1/08/490/005
EU/1/08/490/006
EU/1/08/490/007
EU/1/08/490/008
EU/1/08/490/019
EU/1/08/490/020

Pramipexole Teva 0.35 mg tablets
EU/1/08/490/009
EU/1/08/490/010
EU/1/08/490/011
EU/1/08/490/012
EU/1/08/490/021
EU/1/08/490/022

Pramipexole Teva 0.7 mg tablets
EU/1/08/490/013
EU/1/08/490/014
EU/1/08/490/015
EU/1/08/490/016
EU/1/08/490/023
EU/1/08/490/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2008
Date of latest renewal: 26 August 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 manufacturer responsible for batch release

Teva Pharmaceutical Works Co. Ltd.
Pallagi Street 13
H-4042 Debrecen
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő,
Táncsics Mihály út 82
Hungary

TEVA UK Ltd
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

Pharmachemie B.V.
Swensweg 5,
Postbus 552,
2003 RN Haarlem
The Netherlands

GALIEN LPS
98 rue Bellocier
89100 Sens
France

Teva Czech Industries s.r.o.
Ostravska 29, c.p. 305
747 70 Opava-Komarov
Czech Republic

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

Balkanpharma Dupnitsa AD
3 Samokovsko Shosse Str.,
Dupnitsa 2600,
Bulgaria

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**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Pramipexole Teva 0.088 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 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

Tablets

Blisters:
30 tablets
50 x 1 tablets
100 tablets
30 x 1 tablets
100 x 1 tablets

Tablet container:
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/001
EU/1/08/490/002
EU/1/08/490/003
EU/1/08/490/004
EU/1/08/490/017
EU/1/08/490/018

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Teva 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 - Pramipexole Teva 0.088 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.088 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS

Self-adhesive, paper label -Pramipexole Teva 0.088 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.088 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/004

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Pramipexole Teva 0.18 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 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

Tablets

Blisters:
30 tablets
50 x 1 tablets
100 tablets
30 x 1 tablets
100 x 1 tablets

Tablet container:
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use

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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/005
EU/1/08/490/006
EU/1/08/490/007
EU/1/08/490/008
EU/1/08/490/019
EU/1/08/490/020

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Teva 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 – Pramipexole Teva 0.18 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.18 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS

self-adhesive, paper label - Pramipexole Teva 0.18 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 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

Tablets

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/008

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Pramipexole Teva 0.35 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 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

Tablets

Blisters:
30 tablets
50 x 1 tablets
100 tablets
30 x 1 tablets
100 x 1 tablets

Tablet container:
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25°C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/009
EU/1/08/490/010
EU/1/08/490/011
EU/1/08/490/012
EU/1/08/490/021
EU/1/08/490/022

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pramipexole Teva 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 – Pramipexole Teva 0.35 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.35 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS

Self-adhesive, paper label – Pramipexole Teva 0.35 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 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

Tablets

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/012

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Pramipexole Teva 0.7 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.7 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Blisters:
30 tablets
50 x 1 tablets
100 tablets
30 x 1
100 x 1

Tablet container:
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/013
EU/1/08/490/014
EU/1/08/490/015
EU/1/08/490/016
EU/1/08/490/023
EU/1/08/490/024

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

Pramipexole Teva 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 – Pramipexole Teva 0.7 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.7 mg tablets
Pramipexole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

Not applicable

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING UNITS

self-adhesive, paper label - Pramipexole Teva 0.7 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Pramipexole Teva 0.7 mg tablets
Pramipexole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. 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

Do not store above 25 °C.
Store in the original package in order to protect from light and 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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/490/016

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PRAMIPEXOLE TEVA 0.088 MG TABLETS
PRAMIPEXOLE TEVA 0.18 MG TABLETS
PRAMIPEXOLE TEVA 0.35 MG TABLETS
PRAMIPEXOLE TEVA 0.7 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 Teva is and what it is used for

Pramipexole Teva 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 Teva 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 Teva

Do not take Pramipexole Teva:
- 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 Teva. 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 Teva.
- 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 Teva.
- 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, 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 Teva treatment. If the problems persist more than a few weeks, your doctor may need to adjust your treatment.

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

Other medicines and Pramipexole Teva
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 Teva 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 Teva.

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 Teva may affect your ability to drive and operate machinery.

Pramipexole Teva with food, drink and alcohol
You should be cautious while drinking alcohol during treatment with Pramipexole Teva.
Pramipexole Teva 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 Teva.

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

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

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

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

Pramipexole Teva 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 Teva

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 Teva with or without food. Swallow the tablets with water.

The daily dose is to be taken divided into 3 equal doses.

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

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

	Lowest maintenance dose	Highest maintenance dose

Number of tablets	1 tablet Pramipexole Teva 0.088 mg three times a day	1 tablet containing 1.1 mg pramipexole 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 Pramipexole Teva 0.088 mg twice a day. In severe kidney disease, the usual starting dose is just 1 tablet Pramipexole Teva 0.088 mg a day.

If you take more Pramipexole Teva 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 Teva
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 Teva
Do not stop taking Pramipexole Teva 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.

You should not stop treatment with Pramipexole Teva 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

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 Teva 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 Pramipexole Teva

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.

Do not store above 25 ºC.
Store in the original package in order to protect from light and moisture.

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 Pramipexole Teva contains

The active substance is pramipexole.

Each tablet contains 0.088 mg, 0.18 mg, 0.35 mg, or 0.7 mg pramipexole as 0.125 mg, 0.25 mg, 0.5 mg, or 1 mg pramipexole dihydrochloride monohydrate, respectively.

The other ingredients are mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate, sodium stearyl fumarate, colloidal silicon dioxide.

What Pramipexole Teva looks like and contents of the pack
- Pramipexole Teva 0.088 mg tablets are white, round tablets, embossed with "93" on one side and "P1" on the other side.
- Pramipexole Teva 0.18 mg tablets are white round, scored tablets embossed with "P2" over "P2" on the scored side and "93" on the other side. The tablet can be divided into equal halves.
- Pramipexole Teva 0.35 mg tablets are white, oval, biconvex tablets, engraved with 9 vertical scoreline 3 on the scored side, and 8023 on the other side. The tablet can be divided into equal halves.
- Pramipexole Teva 0.7 mg tablets are white, round, scored tablets embossed with "8024" over "8024" on the scored side and "93" on the other side. The tablet can be divided into equal halves.
- Pramipexole Teva tablets are available in blister packs of 30, 30 x 1, 50 x 1, 100 x 1 and 100 tablets and bottles containing 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

Manufacturer
TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13,
4042 Debrecen,
Hungary

Or:

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő,
Táncsics Mihály út 82
Hungary

Or:

TEVA UK Ltd
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

Or:

Pharmachemie B.V.
Swensweg 5,
Postbus 552,
2003 RN Haarlem
The Netherlands

Or:

GALIEN LPS
98 rue Bellocier
89100 Sens
France

Or:

Teva Czech Industries s.r.o
Ostravska 29, c.p. 305
747 70 Opava-Komarov
Czech Republic

Or:

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

Or:

Balkanpharma Dupnitsa AD
3 Samokovsko Shosse Str.,
Dupnitsa 2600,
Bulgaria

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A.
Tel/Tél: +32 3 820 73 73

България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland
Teva GmbH
Tel: +49 731 402 08

Eesti
Teva Eesti esindus UAB Sicor Biotech
Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς Α.Ε.
Τηλ: +30 210 72 79 099

España
Teva Pharma, S.L.U
Tél: +(34) 91 387 32 80

France
Teva Santé
Tél: +(33) 1 55 91 7800

Hrvatska
Pliva Hrvatska d.o.o.
Tel:+ 385 1 37 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 (0)51 321 740

Ísland
ratiopharm Oy
Finnland
Puh/Tel: +358 20 180 5900

Italia
Teva Italia S.r.l.
Tel:. +39 028917981

Lietuva
UAB “Sicor Biotech”
Tel: +370 5 266 02 03

Luxembourg/Luxemburg
ratiopharm GmbH
Allemagne/Deutschland
Tél: +49 731 402 02

Magyarország
Teva Gyógyszergyár Zrt. Tel.: +36 1 288 64 00

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +353 51 321740

Nederland
Teva Nederland B.V.
Tel: +31 (0) 800 0228400

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
TeI.Nr.: +43/1/97007-0

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +(48) 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos Lda
Tel: (351) 21476 75 50

România
Teva Pharmaceuticals S.R.L
Tel: +4021 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +(421) 2 5726 7911

Suomi/Finland
ratiopharm Oy
Puh/Tel: +358 20 180 5900

Κύπρος
Teva Ελλάς Α.Ε.
Ελλάδα
Τηλ: +30 210 72 79 099

Latvija
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 323666

Sverige
Teva Sweden AB
Tel: +(46) 42 12 11 00

United Kingdom
Teva UK Limited
Tel: +(44) 1977 628 500

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