SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RAMIPEX 1 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

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

NOTE:

Pramipexole doses published in the literature refer to the salt form. Therefore, doses are presented in both the pramipexole salt form and the base form (in parentheses).

Excipients:

For a complete list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, scored tablets

The tablets can be divided into two equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAMIPEX is indicated for the treatment of symptoms and signs of idiopathic Parkinson's disease in adults. It can be used alone (without levodopa) or in combination with levodopa during the course of the disease, as levodopa's effect begins to wane or fluctuate in the later stages (end-of-dose or on/off fluctuations).

RAMIPEX is indicated for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in adults at doses up to 0.75 mg (salt) (0.54 mg base) (see Section 4.2).

4.2 Posology and method of administration

Parkinson's disease

Dosage/administration frequency and duration:

The daily dose is administered three times daily, divided into three equal parts.

Initial treatment:

The dose should be increased stepwise every 5-7 days, starting from an initial dose of 0.375 mg (salt) per day (0.264 mg base). The dose should be titrated until the maximum therapeutic effect is achieved, provided that no intolerable adverse effects occur in patients.

RAMIPEX Dose Escalation Schedule				
Week	Dose (mg, base)	Total daily dose (mg, base)	Dose (mg, salt)	Total daily dose (mg, salt)
1	3x0.088	0.264	3x0.125	0.375
2	3x0.18	0.54	3x0.25	0.75
3	3x0.35	1.1	3x0.5	1.5

RAMIPEX 1 mg Tablets are scored and can be divided into two equal parts. Thus, the 0.125 mg dose shown in the diagram above can be obtained by splitting a 0.25 mg tablet in half.

If further dose escalation is necessary, the daily dose should be increased by 0.75 mg salt (0.54 mg base) at weekly intervals. The maximum daily dose is 4.5 mg salt (3.3 mg base). However, it should be noted that the incidence of somnolence increases at doses above 1.5 mg salt (1.1 mg base) per day (see Section 4.8).

Maintenance therapy:
Daily individual pramipexole doses should range from 0.375 mg salt (0.264 mg base) to a maximum of 4.5 mg salt (3.3 mg base). During dose escalation in the pivotal clinical trials, efficacy was observed when starting at a dose of 1.5 mg salt per day (1.1 mg base). Further dose adjustments should be made based on clinical response and adverse reactions. In clinical studies, approximately 5% of patients were treated with doses below 1.5 mg salt (1.1 mg base). In advanced stages of Parkinson's disease, pramipexole doses above 1.5 mg salt (1.1 mg base) per day may be beneficial for patients in whom levodopa therapy is to be reduced. During both dose escalation and maintenance therapy with RAMIPEX, a reduction in levodopa dose is recommended based on the individual patient's response (see Section 4.5).

Discontinuation of treatment:
Sudden discontinuation of dopaminergic therapy may lead to neuroleptic malignant syndrome or dopamine agonist
withdrawal syndrome.

Pramipexole should be discontinued gradually, starting with a daily dose of 0.75 mg salt (0.54 mg base), then reducing by 0.75 mg salt (0.54 mg base) daily, and finally reducing by 0.375 mg salt (0.264 mg base) daily (see Section 4.4). During gradual discontinuation, dopamine agonist withdrawal syndrome may still develop, and a temporary increase in dose may be necessary before restarting the dose reduction process (see Section 4.4).

Administration:

Tablets should be taken orally and swallowed with water. Tablets may be taken with or without food.

Additional information for specific populations:
Renal impairment:
The elimination of pramipexole is dependent on renal function. The following dosage regimen is recommended when initiating treatment:

In patients with creatinine clearance above 50 mL/min, no reduction in daily dose or dosing frequency is necessary.

In patients with creatinine clearance between 20-50 mL/min, the initial daily dose of RAMIPEX tablets should be administered in two divided doses, starting with 0.125 mg salt (0.088 mg base) twice daily (0.25 mg/day salt / 0.176 mg/day base). The maximum daily dose of 2.25 mg pramipexole salt (1.57 mg base) should not be exceeded.

In patients with creatinine clearance below 20 mL/min, the daily dose of RAMIPEX tablets should be administered as a single daily dose and should be started at 0.125 mg salt (0.088 mg base) per day. The maximum daily dose of 1.5 mg pramipexole salt (1.1 mg base) should not be exceeded.

If renal function decreases during maintenance therapy, the daily dose of RAMIPEX should be reduced in proportion to the decrease in creatinine clearance. That is, if creatinine clearance decreases by 30%, the daily dose of RAMIPEX should also be reduced by 30%. If creatinine clearance is between 20-50 mL/min, the daily dose is administered in two divided doses, and if creatinine clearance is below 20 mL/min, it is administered as a single daily dose.

Hepatic impairment:
Dose reduction is probably not necessary in patients with hepatic impairment, as approximately 90% of the absorbed active substance is excreted via the kidneys. However, the potential effect of hepatic impairment on the pharmacokinetics of RAMIPEX has not been studied.

Pediatric population:
The efficacy and safety of RAMIPEX in children under 18 years of age have not been established. There is no indication for the use of RAMIPEX in the pediatric population for Parkinson's disease.

Geriatric population:
The elimination half-life of RAMIPEX is longer in the elderly (see Section 5.2).

Restless legs syndrome (RLS)

Dosage/frequency and duration of administration:

The recommended starting dose of RAMIPEX is 0.125 mg salt (0.088 mg base) taken once daily, 2-3 hours before bedtime. In patients requiring further symptomatic improvement, the dose may be increased every 4-7 days up to a maximum of 0.75 mg salt (0.54 mg base) per day (as shown in the table below). The lowest effective dose should be used (see Section 4.4 *Restless Legs Syndrome*).

RAMIPEX Dosage Schedule		
Titration phase	Once daily, evening dose (mg, base)	Once daily, evening dose (mg, salt)
1	0.088	0.125
2	0.18	0.25
3*	0.35	0.5
4*	0.54	0.75

*If necessary

After three months of treatment, the patient's response should be evaluated and the need for continued treatment should be reassessed. If treatment has been interrupted for more than a few days, the dosage titration given above should be applied when restarting treatment.

Discontinuation of treatment:

Since the daily dose in Restless Legs Syndrome treatment will not exceed 0.75 mg of salt (0.54 mg base), RAMIPEX can be discontinued without stepwise dose reduction. In a 26-week placebo-controlled clinical trial, after pramipexole was abruptly discontinued, Restless Legs Syndrome symptoms reappeared (rebound; worsening of symptom severity compared to baseline) in 10% of patients (14 out of 135 patients). This effect was found to be similar across all dose levels.

Administration:

Tablets should be taken orally and swallowed with water. Tablets may be taken with or without food.

Additional information for specific populations:

Renal impairment:

The elimination of pramipexole is dependent on renal function. No reduction in daily dose is necessary in patients with creatinine clearance above 20 mL/min.

No studies have been conducted on the use of RAMIPEX in hemodialysis patients or patients with severe renal impairment.

Hepatic impairment:

Since approximately 90% of the absorbed active ingredient is excreted via the kidneys, no dose reduction is necessary in patients with hepatic impairment.

Pediatric population:
As there is no data on safety and efficacy, the use of RAMIPEX is not recommended in children and adolescents under 18 years of age.

Geriatric population:
The elimination half-life of RAMIPEX is longer in the elderly (see Section 5.2).

Tourette's disorder
Pediatric population:
As safety and efficacy have not been established in this population, the use of RAMIPEX is not recommended in children and adolescents under 18 years of age. Due to the negative benefit-risk balance in this condition, RAMIPEX should not be used in children and adolescents with Tourette's disorder (see Section 5.1).

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 RAMIPEX to a Parkinson's patient with renal impairment, a dose reduction as described in Section 4.2 is recommended.

Hallucinations
Hallucinations are known to be a side effect of dopamine agonists and levodopa treatments. Patients should be informed that hallucinations (mostly visual) may occur.

Dyskinesia
In combination therapy with levodopa in advanced Parkinson's disease, dyskinesia may occur during the initial titration of RAMIPEX. If dyskinesia occurs, the levodopa dose should be reduced.

Dystonia
Following initiation or dose increase of pramipexole, axial dystonia, including antecollis, camptocormis, and pliotonus (Pisa Syndrome), has been reported rarely in patients with Parkinson's disease. Although dystonia can be a symptom of Parkinson's disease, symptoms in these patients have resolved after pramipexole was reduced or withdrawn. If dystonia occurs, dopaminergic drug therapy should be reviewed and an adjustment in the pramipexole dose should be considered.

Sudden sleep onset and somnolence

Pramipexole has been associated with episodes of somnolence and sudden sleep onset, particularly in patients with Parkinson's disease. Sudden sleep onset during daily activities has been reported with uncommon frequency; in some cases, this may occur without awareness or warning signs. Patients should be informed about this and advised to be cautious when driving or operating machinery during RAMIPEX treatment. Patients who experience somnolence and/or sudden sleep episodes should refrain from activities such as driving or operating machinery. In addition, dose reduction or discontinuation of treatment may be considered. Due to possible additive effects, patients should be warned to be cautious if they are taking other sedative medications or alcohol in combination with pramipexole (see Sections 4.5, 4.7, and 4.8).

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and those involved in their care and treatment should be informed that behavioral symptoms of impulse control disorders, such as pathological gambling, increased libido, hypersexuality, compulsive spending or shopping, binge eating, and compulsive eating, may occur in patients treated with dopamine agonists, including RAMIPEX. If such symptoms develop, a reduction in dose or gradual discontinuation should be considered.

Mania and delirium

Patients should be monitored regularly for the risk of developing mania and delirium. Patients and caregivers should be warned that mania and delirium may occur in patients treated with pramipexole. If such symptoms develop, dose reduction/gradual dose reduction and discontinuation of the drug should be considered.

Patients with psychotic disorders

Patients with psychotic disorders should only be treated with dopamine agonists when the potential benefits outweigh the risks. The concomitant use of antipsychotic medications with pramipexole should be avoided (see Section 4.5).

Ophthalmological monitoring

Ophthalmological monitoring is recommended at regular intervals or if visual abnormalities occur.

Severe cardiovascular disease

Caution is advised in cases of severe cardiovascular disease. Due to the risk of postural hypotension generally associated with dopaminergic therapy, monitoring of blood pressure is recommended, especially at the start of treatment.

Neuroleptic malignant syndrome

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt discontinuation of dopaminergic therapy (see Section 4.2).

Dopamine agonist discontinuation syndrome
Dopamine agonist withdrawal syndrome has been reported with dopamine agonists, including pramipexole (see Section 4.8). In Parkinson's disease patients, pramipexole should be tapered off gradually when discontinuing treatment (see Section 4.2). Limited data suggest that the risk of developing dopamine agonist discontinuation syndrome may be higher in patients with impulse control disorders and in patients receiving dopamine agonists at high daily doses and/or high cumulative doses. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating, and pain, and do not respond to levodopa. Before discontinuing pramipexole by gradual reduction, patients should be informed about withdrawal symptoms. Patients should be closely monitored during gradual dose reduction and discontinuation. If severe and/or persistent withdrawal symptoms occur, temporary administration of pramipexole at the lowest effective dose may be considered.

Worsening of restless legs syndrome
Treatment with pramipexole in restless legs syndrome may result in worsening of the disease. Worsening of the disease is defined as symptoms starting earlier in the evening (or even in the afternoon), increased symptoms, and spread of symptoms to other extremities. The risk of worsening may increase with higher doses. Before treatment, patients should be informed that worsening of the disease may occur and advised to contact their doctor if they experience signs of worsening. If worsening of the disease is suspected, the pramipexole dose should be adjusted to the lowest effective dose or pramipexole should be discontinued (see Sections 4.2 and 4.8).

4.5 Interactions with other medicinal products and other forms of interaction
Plasma protein binding
Pramipexole binds to plasma proteins at a very low level (<20%) and undergoes minimal biotransformation in humans. Therefore, the potential for interactions with other drugs that affect plasma protein binding or elimination via biotransformation is negligible. Since anticholinergic drugs are primarily eliminated via biotransformation, the potential for interaction is limited; however, interactions with anticholinergics have not been studied. There are no pharmacokinetic interactions with selegiline and levodopa.

Active renal elimination pathway inhibitors/competitors
Cimetidine, probably by inhibiting the cationic secretory transport system in the renal tubules, reduced the renal clearance of pramipexole by approximately 34%. Therefore, drugs that inhibit this active renal elimination pathway, or are eliminated via this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole and cause a decrease in pramipexole clearance. When these drugs are administered concomitantly with RAMIPEX, a reduction in the pramipexole dose should be considered.

Combination with levodopa
When RAMIPEX is administered in combination with levodopa, a reduction in the levodopa dose is recommended, and when the RAMIPEX dose is increased, the doses of other antiparkinsonian drugs should be maintained.

Due to the possibility of additive effects, patients should be advised to exercise caution when taking other sedative medications or alcohol in combination with pramipexole (see Sections 4.4, 4.7, and 4.8).

Antipsychotic medications
The use of antipsychotic medications in combination with pramipexole should be avoided (see Section 4.4); for example, when antagonistic effects are anticipated.

Additional information for specific populations:
No specific data are available.

Pediatric population:
No specific data is available.

4.6 Pregnancy and lactation
General recommendation:
Pregnancy category C.

Women of childbearing potential/Birth control (Contraception)
Women of childbearing potential should use medically effective birth control methods during treatment.

Pregnancy
The effects on pregnancy and lactation in humans have not been studied.

Pramipexole has not shown teratogenic effects in rats and rabbits, but has shown embryotoxic effects in rats at maternotoxic doses (see Section 5.3).
RAMIPEX should not be used during pregnancy unless clearly necessary; it should only be used when the potential benefits outweigh the potential risk to the fetus.

Lactation
Due to the inhibition of prolactin secretion by pramipexole treatment in humans, inhibition of lactation is expected. The passage of pramipexole into human milk has not been studied. In rats, the concentration of radioactivity of the active substance in milk was found to be higher than in plasma.

Due to the lack of data in humans, RAMIPEX should not be used during breastfeeding. However, if its use cannot be avoided, breastfeeding should be discontinued.

Reproductive ability/Fertility
No studies have been conducted on human fertility. In animal studies, pramipexole, as expected from a dopamine agonist, affected estrus cycles and reduced female fertility. However, these studies did not show any direct or indirect harmful effects on male fertility.

4.7 Effects on the ability to drive and use machines
RAMIPEX may significantly affect the ability to drive and use machines.

Hallucinations or somnolence may occur.

Patients being treated with RAMIPEX who experience somnolence and/or sudden sleep episodes should be advised to avoid driving or engaging in activities that could put themselves or others at risk of serious injury or death due to lack of attention (e.g., operating machinery) until such recurrent episodes and somnolence have resolved. (See Sections 4.4, 4.5, and 4.8).

4.8 Undesirable effects

According to the analysis of a pool of placebo-controlled studies involving a total of 1,923 patients receiving pramipexole and a total of 1,345 patients receiving placebo, adverse drug reactions were reported frequently in both groups. Sixty-three percent of patients receiving pramipexole and 52% of patients receiving placebo reported at least one adverse drug reaction.

Most adverse drug reactions begin early in treatment and tend to disappear even while treatment continues.
Adverse reactions are listed under the heading of frequency (number of patients expected to experience the reaction) within system-organ classes, using the following frequency categories:
Undesirable effects are classified into frequency groups using the following classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)

The most common adverse reactions in Parkinson's disease
The most common (≥5%) adverse drug reactions reported in Parkinson's disease patients and seen more frequently with pramipexole treatment than with placebo are: nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucinations, headache, and fatigue. The incidence of somnolence increases at doses above 1.5 mg pramipexole salt per

day (see Section 4.2). A more common adverse drug reaction in combination with levodopa is dyskinesia. Hypotension may occur at the start of treatment, especially when pramipexole is titrated too rapidly.

Table 1: Parkinson's disease:

Body system	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000– <1/100)**	**Rare (≥1/10,000- <1/1,000)**	**Not known**
Infections and infestations			Pneumonia		
Endocrine disorders			Inappropriate antidiuretic hormone secretion[1]		
Psychiatric disorders		Insomnia Hallucinations Abnormal dreams Confusion Behavioral symptoms related to impulse control disorders and compulsions	Compulsive shopping Pathological gambling Restlessness Hypersexuality Delusion Libido disorders Paranoia Delirium Binge eating[1] Hyperphagia[1]	Mania	
Nervous system disorders	Somnolence Dizziness Dyskinesia	Headache	Sudden sleepiness Amnesia Hyperkinesis Syncope		
Eye disorders		Visual disturbances including diplopia, blurred vision, and decreased visual			
Cardiac disorders			Heart failure[1]		
Vascular diseases		Hypotension			

Respiratory, chest disorders, and mediastinal diseases			Dyspnea Hiccups		
Gastrointestinal diseases	Nausea	Constipation Vomiting			
Skin and subcutaneous tissue disorders			Hypersensitivity Itching Rash		
Reproductive system and breast				Spontaneous penile erection	
General disorders and disorders related to the application site		Fatigue Peripheral edema			Dopamine agonist withdrawal syndrome, including apathy, anxiety, depression, fatigue, sweating, and pain
Research		Weight loss, including	Weight gain		

[1]This side effect has been observed in post-marketing experience. The 95% confidence interval for the frequency category is greater than "uncommon" but may be lower. Since this side effect was not present in the clinical trial database of 2,762 Parkinson's patients treated with pramipexole, a precise frequency estimate cannot be made.

Most common adverse reactions in restless legs syndrome
The most common (≥5%) adverse drug reactions reported in patients with restless legs syndrome treated with pramipexole are nausea, headache, dizziness, and fatigue. Nausea and fatigue were reported more frequently in female patients treated with pramipexole compared to male patients (20.8% and 10.5% vs. 6.7% and 7.3%, respectively).

Table 2: Restless legs syndrome:

Body system	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000-<1/1,000)	Not known
Infections and infestations			Pneumonia[1]		
Endocrine disorders			Inappropriate antidiuretic hormone secretion[1]		
Psychiatric disorders		Insomnia Abnormal dreams	Restlessness Confusion Hallucinations Libido disorders Delusions[1] Hyperphagia[1] Paranoia[1] Mania[1] Delirium[1] Impulse control disorders and behavioral symptoms related to compulsions (e.g., compulsive shopping, pathological gambling, hypersexuality, binge eating)		
Nervous system disorders	Increased restless legs syndrome	Headache, dizziness, somnolence	Sudden sleep onset Syncope Dyskinesia Amnesia[1] Hyperkinesis[1]		
Eye disorders			Visual disturbances including diplopia, blurred vision, and decreased visual acuity		

Cardiac disorders			Heart failure[1]		
Vascular diseases			Hypotension		
Respiratory, chest disorders, and mediastinal diseases			Dyspnea Hiccups		
Gastrointestinal diseases	Nausea	Constipation Vomiting			
Skin and subcutaneous tissue disorders			Hypersensitivity Itching Rash		
Reproductive system and breast disorders				Spontaneous penile erection	
General disorders and disorders related to the application site		Fatigue	Peripheral edema		Dopamine agonist withdrawal syndrome, including apathy, anxiety, depression, fatigue, sweating, and pain
Investigations			Weight loss, including decreased appetite Weight gain		

[1]This side effect has been observed in post-marketing experience. The 95% confidence interval for the frequency category is greater than "uncommon" but may be lower. Since this side effect was not present in the clinical trial database of 1,395 restless legs syndrome

patients treated with pramipexole, it is not possible to make a definitive estimate of its frequency.

Description of selected adverse reactions

Somnolence
Pramipexole is commonly associated with somnolence and is less commonly associated with excessive daytime somnolence and sudden sleep episodes (see Section 4.4).

Libido disorders
Pramipexole may be associated with libido disorders (increase or decrease) at an uncommon frequency.

Impulse control disorders
In patients treated with dopamine agonists, including RAMIPEX, pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating may occur (see Section 4.4).

In a cross-sectional, retrospective screening and case-control study involving 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms related to an impulse control disorder in the previous six months. Observed symptoms included pathological gambling, compulsive shopping, binge eating, and compulsive sexual behavior (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤65), not being married, and a family history of gambling behavior as reported by the patient.

Dopamine agonist withdrawal syndrome
Non-motor adverse effects may occur when the dose of dopamine agonists, including pramipexole, is reduced or treatment is discontinued. Symptoms include apathy, anxiety, depression, fatigue, sweating, and pain (see Section 4.4).

Heart failure
In clinical studies and post-marketing experience, heart failure has been reported in patients treated with pramipexole. A pharmacoepidemiological study showed that pramipexole use was associated with an increased risk of heart failure compared to no use of this drug (observed risk ratio 1.86; 95% CI, 1.21-2.85).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose

There is no clinical experience with massive overdose. Expected adverse events would be reactions related to the pharmacodynamic profile of a dopamine agonist, such as nausea, vomiting, hyperkinesia, hallucinations, agitation, and hypotension.

There is no specific antidote for dopamine agonist overdose. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Treatment of overdose may require gastric lavage, intravenous fluids, activated charcoal administration, and electrocardiographic monitoring, along with general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Pramipexole, a dopamine agonist, binds with high selectivity and specificity to dopamine D_2family receptors; it shows a preferential affinity for D_3receptors and has full intrinsic activity.

Pramipexole alleviates motor deficits in Parkinson's disease by stimulating dopamine receptors located in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

The mechanism of action of pramipexole in the treatment of restless legs syndrome is unknown. Neuropharmacological data suggest that it primarily interacts with the dopaminergic system.

Pharmacodynamic effects

In studies conducted on volunteers, a dose-dependent decrease in prolactin was observed.

In a clinical study conducted on healthy volunteers, an increase in blood pressure and heart rate was observed when the extended-release tablet formulation of pramipexole was titrated more rapidly than recommended (every 3 days) up to 4.5 mg pramipexole salt per day (3.15 mg base). Such an effect has not been observed in studies conducted on patients.

Clinical efficacy and safety in Parkinson's disease

Pramipexole treatment alleviates the signs and symptoms of idiopathic Parkinson's disease. Approximately 1,800 Hoehn and Yahr stage I-IV patients were treated with pramipexole in

placebo-controlled clinical trials. Approximately 1,000 of these patients were in more advanced stages, were receiving concomitant levodopa therapy, and had developed motor complications.

In controlled clinical trials conducted in the early and advanced stages of Parkinson's disease, the efficacy of pramipexole was sustained for approximately six months. In open-label maintenance studies lasting longer than three years, there was no indication of a decline in efficacy.

In a two-year, controlled, double-blind clinical trial, 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 weighed against the greater improvement in motor function seen with levodopa (as measured by the mean change in UPDRS score). The overall incidence of hallucinations and somnolence is generally higher in the pramipexole group during the dose escalation phase; however, there is no significant difference during the maintenance period. These points should be considered when initiating pramipexole treatment in Parkinson's disease patients.

Pediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with pramipexole in all subsets of the pediatric population for Parkinson's disease (for information on pediatric use, see Section 4.2).

Clinical efficacy and safety in restless legs syndrome
The efficacy of pramipexole was evaluated in approximately 1,000 patients with moderate to severe idiopathic restless legs syndrome in four placebo-controlled clinical studies.

The mean change from baseline in the Restless Legs Syndrome Rating Scale (IRLS) and Clinical Global Impression of Improvement (CGI-I) are the primary efficacy outcome measures. In both primary endpoints, statistically significant differences were observed in the pramipexole dose groups (0.25 mg, 0.5 mg, and 0.75 mg pramipexole salt) compared to placebo. After 12 weeks of treatment, the baseline IRLS score improved from 23.5 to 14.1 points with placebo and from 23.4 to 9.4 points with pramipexole (doses combined). The adjusted mean difference was -4.3 points (95% CI: -6.4 to -2.1 points, p-value <0.0001). CGI-I responder rates (improvement, much improvement) were 51.2% and 72% for placebo and pramipexole, respectively (20% difference, 95% CI: 8.1%-31.8%, p<0.0005). Efficacy was observed after the first week of treatment with 0.125 mg salt (0.088 mg base) daily.

In a three-week, placebo-controlled polysomnography study, pramipexole significantly reduced the number of periodic leg movements during time spent in bed.

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

Pediatric population

The European Medicines Agency has deferred the requirement to submit results from studies with pramipexole in one or more subsets of the pediatric population for restless legs syndrome (for information on pediatric use, see Section 4.2).

Clinical efficacy and safety in Tourette's disorder

The efficacy of pramipexole (0.0625-0.5 mg/day) in pediatric patients aged 6-17 years with Tourette syndrome was evaluated in a 6-week, double-blind, randomized, placebo-controlled, flexible-dose study. A total of 63 patients were randomized (43 patients to pramipexole, 20 patients to placebo). The primary endpoint was the change in the Total Tic Score (TTS) on the Yale Global Tic Severity Scale (YGTSS) from baseline. Compared to placebo, pramipexole did not show a significant difference for either the primary endpoint or any of the secondary efficacy endpoints (including YGTSS total score, Patient Global Impression of Improvement (PGI-I), Clinician Global Impression of Improvement (CGI-I), or Clinician Global Impression of Severity (CGI-S)). Adverse events occurring in at least 5% of patients in the pramipexole group and observed more frequently in patients treated with pramipexole than in those receiving placebo are as follows: headache (27.9%, placebo 25%), somnolence (7%, placebo 5%), nausea (18.6%, placebo 10%), vomiting (11.6%, placebo 0%), upper abdominal pain (7%, placebo 5%), orthostatic hypotension (9.3%, placebo 5%), myalgia (9.3%, placebo 5%), sleep disorder (7%, placebo 0%), dyspnea (7%, placebo 0%), and upper respiratory tract infection (7%, placebo 5%). Other important adverse events leading to discontinuation of the study drug in patients receiving pramipexole included confusional state, speech disorder, and worsening of the clinical condition (see Section 4.2).

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Pramipexole is rapidly and completely absorbed following oral administration. Absolute bioavailability is greater than 90%, and maximum plasma concentrations are reached within 1 to 3 hours. Administration with food does not reduce the amount of pramipexole absorbed, but it does reduce the rate of absorption.

Distribution:

In humans, pramipexole has very low protein binding (<20%) and a high volume of distribution (400 L). High concentrations have been observed in brain tissue in rats (approximately 8 times higher than in plasma).

Biotransformation:
Pramipexole is metabolized only to a small extent in humans.

Elimination:
Excretion of unchanged pramipexole via the kidneys is the major route of elimination.[14]Approximately 90% of a C-labeled dose is excreted by the kidneys, while less than 2% is found in feces. The total clearance of pramipexole is around 500 mL/min, and the renal clearance is around 400 mL/min. The elimination half-life (t½) varies from 8 hours in young people to 12 hours in the elderly.

Linearity/Nonlinearity:
Pramipexole exhibits linear kinetics, and inter-patient variation in plasma levels is low.

Characteristic features in patients
Age:
Pediatric population: The efficacy and safety of pramipexole in children and adolescents up to 18 years of age have not been established.

Geriatric population: Pramipexole has a longer elimination half-life in the elderly.

Renal impairment:
The elimination of pramipexole is dependent on renal function and is closely related to creatinine clearance.

Based on a pharmacokinetic study conducted in patients with renal impairment, no reduction in daily dose is necessary in patients with restless legs syndrome who have a creatinine clearance above 20 mL/min (see Section 4.2 for details).

Hepatic impairment:
The potential effect of hepatic impairment on the pharmacokinetics of pramipexole has not been studied. However, dose reduction is not considered necessary in patients with hepatic impairment, as approximately 90% of the absorbed active substance is excreted via the kidneys.

5.3 Preclinical safety data
Repeated dose toxicity studies have shown that pramipexole causes functional effects primarily in the central nervous system and female reproductive system, likely due to the exaggerated pharmacodynamic effects of pramipexole.

In minipigs, decreases in diastolic and systolic pressure and heart rate were recorded; a tendency toward hypotensive effects was also revealed in monkeys.

The potential effects of pramipexole on reproductive functions have been investigated in rats and rabbits. Pramipexole is not teratogenic in rats and rabbits, but it has shown embryotoxic effects in rats at maternotoxic doses. Due to the limited selection of animal species and parameters studied, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

Delayed sexual development has been observed in rats (i.e., separation of the prepuce and opening of the vagina). The relevance of this finding to humans is unknown.

Pramipexole is not genotoxic. In a carcinogenicity study, Leydig cell hyperplasia and adenomas developing in male rats were explained by the prolactin-inhibiting effect of pramipexole. This finding has no clinical relevance for humans. This study also found that pramipexole (salt form) at doses of 2 mg/kg and higher was associated with retinal degeneration in albino rats. This finding was not observed in pigmented rats, in a 2-year carcinogenicity study in albino mice, or in other species studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Mannitol
Povidone
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

Blister packs containing 30 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

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Halkalı Merkez Mah.
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34303 Küçükçekmece/İSTANBUL/TÜRKİYE

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