Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pramipexole Arrow 0.7 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pramipexole Arrow 0.7 mg Tablets contain 0.7 mg of pramipexole base (as 1.0 mg of pramipexole dihydrochloride monohydrate).

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, flat-faced, bevel-edged tablet with “PM4/PM4 ” on one side and “>|>” on the other side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pramipexole Arrow Tablets are indicated 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

Parkinson’s disease

The tablets should be taken orally, swallowed with water, and can be taken either with or without food. The daily dosage is administered in equally divided doses 3 times a day.

Initial treatment:

Dosages 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 unacceptable side-effects, the dosage should be titrated to achieve the optimal therapeutic effect.

Ascending - Dose Schedule of Pramipexole Arrow Tablets

Week	Dosage (mg of base)	Total Daily Dose (mg of base)	Dosage (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 three 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 undesirable effects. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, pramipexole doses higher than 1.1 mg (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 dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with Pramipexole Arrow Tablets, depending on reactions in individual patients.

Treatment discontinuation:

Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Therefore, 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).

Dosing in patients with renal impairment:

The elimination of pramipexole is dependent on renal function. The following dosage 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 Arrow Tablets 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 Arrow Tablets 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, reduce Pramipexole Arrow Tablets daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the Pramipexole Arrow Tablets daily dose 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.

Dosing in patients with 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 pharmacokinetics has not been investigated.

Paediatrics population

The safety and efficacy of Pramipexole Arrow Tablets in children below 18 years has not been established. There is no relevant use of Pramipexole Arrow Tablets in the paediatrics population in Parkinson's disease.

Tourette disorder

Paediatric population

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

When prescribing Pramipexole Arrow Tablets 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 Arrow Tablets. If they occur, the dose of levodopa should be decreased.

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 Arrow Tablets. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage 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 section 4.5, 4.7 and section 4.8).

Impulse control disorders and compulsive behaviours
Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Furthermore, patients and caregivers should be aware of the fact that other behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/taper discontinuation should be considered.

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).

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 anticholiergics 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, and amantadine and mexiletine, may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole Arrow Tablets.

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

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 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

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

As Pramipexole Arrow Tablets 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 Arrow Tablets should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

Fertility
No human or non clinical fertility data are available.

4.7 Effects on ability to drive and use machines

Pramipexole Arrow Tablets can have a major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with Pramipexole Arrow Tablets 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

Expected adverse reactions
The following adverse reactions are expected under the use of pramipexole: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, peripheral oedema, pneumonia, paranoia; pruritis, rash and other hypersensitivity; restlessness somnolence, sudden onset of sleep; syncope, visual disturbance including vision blurred and visual acuity reduced, vomiting, weight decrease, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on pramipexole and 1354 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.

Table 1 displays the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease. The adverse drug reactions reported in this table are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. However, the majority of common adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was 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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Parkinson's disease, most common adverse events
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 :

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	Pneumonia
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions, confusion, hallucinations, insomnia, restlessness
Uncommon	compulsive shopping, delusion, hypersexuality, libido disorder, paranoia, pathological gambling
Not known	binge eating, hyperphagia
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	amnesia, headache
Uncommon	hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual disturbance including vision blurred and visual acuity reduced
Vascular disorders	
Very common	hypotension

Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
General disorders and administration site conditions	
Common	fatigue, peripheral oedema
Investigations	
Common	weight decrease
Uncommon	weight increase

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 and compulsive behaviours
Patients treated with dopamine agonists for Parkinson's disease, including pramipexole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. See also section 4.4.

In a cross-sectional, retrospective screening and case-control study including 3090 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.

4.9 Overdose

There is no clinical experience with massive over dosage. The expected adverse events 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 over dosage 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: dopamine agonists, ATC code: N04BC05

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which it has a preferential affinity to D3 receptors, and has full intrinsic activity.

Pramipexole alleviates Parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

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 trials in Parkinson's disease

In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease.

Placebo controlled clinical trials included approximately 1800 patients of Hoehn and Yahr stages I – V treated with pramipexole. Out of these, approximately 1000 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 the controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.

The 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 trial 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

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.

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).

Pramipexole is metabolised in man only to a small extent.

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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize starch
Colloidal Anhydrous Silica
Povidone (K29-32)
Magnesium Stearate

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

6.5 Nature and contents of container

Pramipexol Arrow Tablets are packed in aluminium foil/aluminium foil blister packs.
The pack sizes are 30 or 100 tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow ApS
Sankt Peders Stræde 2, 1
4000 Roskilde
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 1522/5/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th May 2011

10 DATE OF REVISION OF THE TEXT

November 2011