

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 April 2001. For scientific information on procedures after this date please refer to module 8B.

All doses quoted refer to pramipexole base.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity, postural imbalance and tremor. The incidence of PD increases with age and on average, 2 to 3% of the population in the western world will develop PD. The cause of the disease is still unknown. PD develops due to loss of neuronal functions within the basal ganglia and the substantia nigra of the brain. More specifically, there is a marked deficiency in the nigrostriatal dopamine (DA) system due to degeneration of nigral DA neurons. Thus, restoration of the dopaminergic transmission forms the central strategy for the treatment of PD.

Levodopa (L-dopa) in combination with a peripheral dopa decarboxylase inhibitor (DDI) is the standard treatment of PD. Other treatments include DA agonists and anticholinergic drugs. The ergot derivatives bromocriptine and pergolide are non-selective partial agonists at the DA D2 receptor subfamily (D₂, D₃ and D₄). Such compounds are often given in combination with L-dopa therapy to reduce the dose of the latter thereby increasing treatment tolerability. The response to L-dopa is generally stable during the initial years of treatment. However, due to the progressive degeneration of the DA system, the neuronal buffer capacity is believed to be reduced. At that stage, the patient may switch within seconds from a state of relatively good mobility to one of severe Parkinsonism, giving rise to the term "on-off" phenomenon. This end-of-dose deterioration implies a shortening of the duration of action of L-dopa. Off periods tend to become longer and to set in abruptly. On periods are often combined with dyskinesias and/or other movement disorders. Furthermore, L-dopa and DA agonist treatments are also associated with other side effects, such as nausea, psychiatric disturbances and cardiovascular effects.

Pramipexole is a synthetic amino-benzothiazole derivative. It has been shown to be a selective and specific full DA receptor agonist with high affinity and selectivity for the DA D2 receptor subfamily, and particularly the D₃ receptor subtype.

Sifrol tablets are indicated for treatment of signs and symptoms of advanced idiopathic Parkinson's disease in combination with levodopa i.e. over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations).

Doses of pramipexole should be titrated to achieve an individual optimal therapeutic response, starting at a daily dose of 0.264 mg (0.375 mg of salt). The individual maintenance dose should be in the range of 0.264 mg (0.375 mg of salt) to a maximum of 3.3 mg (4.5 mg of salt) per day, given in 3 divided doses.

2. Chemical, pharmaceutical and biological aspects

Sifrol is presented as tablets containing pramipexole dihydrochloride monohydrate. There are 5 tablet strengths containing 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, and 1.1 mg of the active substance pramipexole, respectively corresponding to 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, and 1.5 mg of pramipexole dihydrochloride monohydrate. The 5 strengths are differentiated by size, shape and code embossed. The tablets contain mannitol, dried maize starch, colloidal anhydrous silica, and povidone and magnesium stearate. The primary packaging material is a light-protecting polyamide/aluminium/polyvinylchloride blister foil and an aluminium covering foil. Each blister strip contains 10 tablets. There are 2 package sizes, 30 and 100 tablets.

Active substance

Pramipexole is a white to off-white crystalline powder, which is freely soluble in water in a pH-independent way, soluble in methanol, slightly soluble in ethanol and insoluble in dichloromethane. At a relative humidity above 92% it liquefies but at lower relative humidity no absorption of water occurs. The active substance is not light sensitive itself, but has been found to degrade in the tablet matrix or in binary mixtures with each excipient. A variety of degradation products have been identified but the mechanism of degradation is not known. By appropriate light protection during manufacture and by using a light protecting aluminium blister for packaging, photodegradation is avoided.

Pramipexole has one chiral centre and is present as the S-enantiomer. Enantiomeric purity is assured during the synthesis and other enantiomers are not possible.

Pramipexole dihydrochloride monohydrate is synthesised using standard procedures. The chemical structure of pramipexole has been confirmed by elemental analysis, interpreted infra red (IR)-, ultra violet (UV)-, mass spectroscopy-, nuclear magnetic resonance spectra and X-ray diffractometry. Routinely, IR and UV spectra and precipitation of chloride anion are used for identification. The purity is determined by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The enantiomeric purity is controlled by HPLC and by specific optical rotation. Residual solvents are controlled by gas chromatography (GC). All methods were adequately validated.

Pharmaceutical development

The pharmaceutical development conducted by the company resulted in the production of conventional tablets. The tablets, except the lowest strength, have a scoreline. Tablet hardness limits have been set to ensure that tablets may be divided in halves with an acceptable uniformity of content. For the tablets intended to be divided, it has been proven that the tablet halves meet the Ph. Eur. requirements for uniformity of content. The hardness of the tablets has little influence on dissolution, due to the high water solubility of the active substance. Control of tablet hardness during storage is regarded to be sufficient.

Manufacture and control

Throughout the manufacturing processes, relevant, acceptably validated in-process controls are performed. With respect to other ingredients, the tablets contain mannitol as filler, dried maize starch as disintegrant and binder, colloidal anhydrous silica as disintegration promoter and glidant, povidone as binder and magnesium stearate as lubricant. The type of mannitol used has been shown to influence the compression behaviour. Fulfilment of Ph. Eur. requirements has been shown for all excipients used.

Control of the finished product includes assay of active substance, dissolution rate, content uniformity and determination of degradation products, using adequately validated methods. Results from batch analyses showed that all batches complied with release specifications.

Five known impurities including the (R)-enantiomer, one unidentified and acetone (residual solvent) were all qualified at their specification levels.

Stability

In the solid state, the active substance has shown good stability characteristics when tested under a number of different conditions. The proposed limits in the finished product specifications for degradation products as well as the assay-limits (shelf-life) are accepted at present but will be reviewed when data covering the whole shelf life become available. Following packaging of the finished product in the proposed marketing blister, a good stability was demonstrated. A 24-month shelf life is accepted when stored below 30°C and protected from light. Additional results from ongoing stability studies will be submitted when available.

In summary, the chemical and pharmaceutical documentation for pramipexole was considered to be acceptable.

3. Toxicopharmacological aspects

Pharmacodynamics

The pharmacodynamic action of pramipexole has been studied *in vitro* and *in vivo*. In brain homogenates or cell lines expressing cloned human receptors, pramipexole effectively bound to receptors of the DA D2 subfamily (i.e. D₂, D₃ and D₄), with the highest affinity for D₃ binding sites (K_i 0.5 nM). Binding to adrenergic alpha-2, 5HT_{1A} and histamine-2 sites was weak to moderate (K_i > 240 nM). It lacked affinity for binding sites within the DA D1 subfamily (D₁, D₅) and for a large number of centrally acting neurotransmitters. Further *in vitro* studies (e.g. proton generation in a microphysometer assay, stimulation of CHO cell mitogenesis) showed that pramipexole was a full agonist for receptors within the DA D2 subfamily. *In vivo* studies, e.g. electrophysiology, inhibition of prolactin release, DA turnover in specific brain regions, indicated that pramipexole possessed full agonist activity.

Pramipexole was studied in two appropriate animal models of PD. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated monkeys, it dose-dependently antagonised motor deficits and PD-like symptoms. The lowest effective oral dose was 0.053 mg/kg. In rats with unilateral 6-OHDA (6-hydroxydopamine)-induced lesions of the substantia nigra, pramipexole induced contralateral circling. These studies support the dopaminergic activity of pramipexole. At high doses, pramipexole protected DA neurones from degeneration in animal models of ischaemia or metamphetamine-induced neurotoxicity. The clinical relevance of these findings is not known. Taken together, these data provide adequate evidence of pramipexole being a selective and specific full agonist at the DA D2 receptor subfamily acting preferentially via D₃ receptors. Furthermore, activity in relevant animal models of PD was shown.

The general pharmacology program revealed mainly effects related to the primary pharmacological activity of pramipexole. Based on studies with relevant antagonists, these effects were considered to be mediated primarily via DA D2, although a few effects observed at high doses may have been mediated via histamine-2 or alpha-2 receptors. With respect to the CNS, both sedation and stimulation were observed. Furthermore, REM sleep and total sleep time (rat, cat) were reduced in a dose-dependent manner. Pramipexole did not produce extrapyramidal side effects in a monkey model, it was not proconvulsive in mice, and did not affect cocaine self-administration in rats. Pramipexole induced, depending on dose, both hypotensive and hypertensive effects. Respiratory function was not affected in cats. In mice, intestinal passage was moderately slowed and in anaesthetised rats, a slight diuretic and natriuretic effect was observed. Expectedly, pramipexole induced emesis in dogs and decreased prolactin levels in rats as well as in humans. In general, pramipexole in combination with other drugs used for the treatment of PD (L-dopa + carbidopa, selegiline) was well tolerated by monkeys. No additive effects on cardiovascular function were seen in combination with haloperidol. Thus, these studies indicate a favourable general pharmacological profile of pramipexole.

Pharmacokinetics

The pharmacokinetic profile of pramipexole was studied in mouse, rat, rabbit, minipig and monkey, the main species used in the preclinical program. Protein binding was low, < 20% in all species including humans. Distribution studies were conducted in rats with radiolabelled compound. A wide tissue distribution was observed, with up to 9-fold higher tissue exposure to parent compound observed in brain compared to plasma. In pregnant rats, extensive placental transfer to fetuses was observed and in lactating females, levels of drug-related radioactivity in milk were up to 6 times higher than in plasma. After oral administration, absorption was rapid and the bioavailability high (70-90%).

Following oral administration of ¹⁴C-pramipexole, the metabolic pattern was similar in rodents, dog, monkeys and humans. The extent of biotransformation was 20-50% of the dose, comprising mainly of dealkylation, hydroxylation and glucuronide conjugation. The major route of excretion was via the kidney, with 50-80% of the drug-related radioactivity recovered in urine, consisting of the parent compound and 5-8 minor metabolites. The pharmacokinetic profile of pramipexole in rabbits differed from other species, with a slower absorption and a higher degree of biotransformation. Studies in rat plasma as well as in human urine showed that pramipexole does not convert to its R(+)-enantiomer.

Based on pharmacokinetic interspecies comparisons, rat, minipig and monkey were considered as relevant models for human safety assessment.

Toxicology

Single dose toxicity of pramipexole after oral administration was studied in rodents, dogs and monkeys. In rodents, the acute toxicity was considered to be low. Deaths occurred at doses of 70-105 mg/kg and above. CNS-related signs were mainly observed which at high doses included ataxia, dyspnea and tremor/convulsions. Dogs and monkeys also displayed mainly CNS-related signs. In dogs, vomiting occurred at 0.0007 mg/kg and above. Monkeys displayed major excitation at 3.5 mg/kg. There were no indications of target organ or sex-specific toxicity.

Repeated dose toxicity of pramipexole after oral administration was studied in rodents and monkeys (up to 52 week studies) and minipigs (13 weeks). Dogs were not used for long-term studies due to profound emesis caused by pramipexole. All species showed signs of toxicity related to exaggerated pharmacodynamic responses to pramipexole, i.e. stimulation of dopamine D2 receptor subfamily, α -₂ adrenoceptors and/or histamine H₂ receptors. For instance, behavioural changes including hyperactivity were common and lead to a number of secondary effects such as reduced body weights and other stress-induced symptoms. Furthermore, in minipigs and monkeys, pramipexole moderately affected cardiovascular parameters. In rats, the potent prolactin-inhibitory effect of pramipexole affected reproductive organs (e.g. enlarged corpora lutea, pyometra). These findings are well known following DA agonist administration to rats and are considered to be of minor clinical relevance. During long-term exposure of albino rats, a dose-related retinal degeneration was observed. Additional mechanistic studies indicated that simultaneous exposure of albino rats to pramipexole and light caused retinal degeneration. However, this was not observed in pigmented rats, albino mice or other animal species.

Reproductive toxicity studies showed that pramipexole affected oestrous cycles and reduced female fertility as expected for a DA agonist. Male fertility was not affected in a mating study and histopathological evaluation within the toxicological program did not reveal adverse effects on male reproductive organs. Following administration of pramipexole to rats and rabbits during the organogenetic period, no teratogenicity was observed but pramipexole was embryotoxic in rats at maternally toxic dose levels. However, due to the selection of animal models and the limited parameters evaluated in these studies, the potential adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated. Peri-post natal exposure of dams and follow-up of offspring did not reveal any concern. Due to inhibition of prolactin secretion, pramipexole like other DA agonists, is expected to inhibit lactation.

In a standard battery of **in vitro** and **in vivo** genotoxicity tests, pramipexole lacked genotoxic potential. Carcinogenicity was studied in mice and rats following 2 years administration. In male rats, hypertrophy and adenomas of Leydig cells were observed. These changes were considered to be related to the prolactin-inhibiting effect of pramipexole and are known to be a rat-specific response to inhibition of prolactin secretion. Therefore, these findings were not considered to be of concern for human safety

A number of special toxicity studies did not reveal cause for concern with respect to local tolerance, immunotoxicity, drug dependence, and haemolytic or local anaesthetic effects. Intraocular pressure was reduced after topical application to rabbits, which likely was a DA D2 receptor mediated effect.

Summary and conclusion on preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence of pramipexole being a selective and specific full agonist at the DA D2 receptor subfamily acting preferentially via D₃ receptors. Furthermore, activity in relevant animal models of PD has been shown. The general pharmacology program indicated a favourable general pharmacological profile of pramipexole.

Based on pharmacokinetic interspecies comparisons, rat, minipig and monkey were considered as relevant models for human safety assessment. Overall, the toxicology program revealed mainly effects related to the pharmacodynamic action of pramipexole, i.e. affects secondary to its DA agonist activity. Comparisons of plasma concentrations (C_{max}) in all species, at dose levels causing toxicity secondary to the pharmacodynamic activity of pramipexole and following clinical doses to humans revealed narrow or no safety margins. In general, CNS-related toxicity was dose limiting. In addition,

during long-term exposure of albino rats, dose-related retinal degeneration was observed. This information has been included in the Summary of Product Characteristics (SPC).

4. Clinical aspects

The clinical program was aimed at evaluating the efficacy and safety of pramipexole for the treatment of both early and advanced Parkinson's disease. The core clinical documentation consisted of 10 phase II/III trials. Six studies were evaluated for efficacy, of which 5 were considered as main studies and 1 was a trial where pramipexole and bromocriptine were compared with placebo. The remaining 4 were only included in the safety analysis. In addition, 17 phase I trials in female and male healthy volunteers were conducted.

Pharmacodynamics and pharmacokinetics

The pharmacodynamic and pharmacokinetic properties of pramipexole were studied in 17 phase I trials in healthy volunteers (about 200 males and 55 females). Single or repeated oral doses up to 3.2 mg/day were administered in different dosing schedules. Intravenous or transdermal administration was also studied in a small number of subjects.

In single increasing dose tolerance studies, expected pharmacodynamic effects of a DA agonist were demonstrated such as reduced prolactin levels and increased growth hormone levels.

Pharmacokinetic profile

The basic pharmacokinetic profile of pramipexole was adequately described. It was rapidly absorbed with a bioavailability above 90%. The volume of distribution was high (about 400 l) and protein binding was low (<20%). Total body clearance was about 500 ml/min and the elimination half-life ranged from 8 (young) to 12 h (elderly). A linear dose-concentration relationship was shown for doses up to 1.1 mg t.i.d. (3.3 mg).

Elimination

Pramipexole is predominantly (about 90%) excreted unchanged via the kidney. There are indications that pramipexole is secreted via an active transport system for cations, for instance its renal clearance was higher than the glomerular filtration rate. Furthermore, the actively secreted cation cimetidine reduced pramipexole clearance. Thus, other actively secreted cations may interact with the secretion of pramipexole. These possible interactions were not studied but have been adequately addressed in the SPC.

Interactions

Concomitant food intake did not affect the bioavailability of pramipexole. With respect to other types of interactions, the combination L-dopa/carbidopa was studied. Pramipexole increased the rate of levodopa absorption. C_{max} increased by 71% in females and by 13% in males, and T_{max} was reduced by 1.1 (males) to 2.5 h (females). However, the extent of levodopa absorption or elimination was not affected. Safety aspects of this interaction are addressed in the section on Clinical Safety.

Special populations

Not unexpectedly, the elimination of pramipexole was reduced in patients with impaired renal function. It was concluded that the dose should be reduced by the same percentage as the decline in creatinine clearance. Furthermore, the renal clearance of pramipexole was about 20% lower in women and elderly than in young male subjects. However, special dose recommendations for women or elderly are not considered necessary since dose titration is made on an individual basis. Patients with hepatic impairment were not studied which is acceptable since pramipexole is predominantly excreted unchanged.

Bioequivalence

The tablet formulations used in the main clinical trials and the final formulations intended for marketing were bioequivalent with respect to area under the plasma concentration-time curve (AUC), maximum and minimum plasma concentrations at 8 h (C_{max}, C_{min8h}) and the time to reach C_{max} (T_{max}).

Therapeutic efficacy

In advanced PD patients, the core clinical documentation consisted of 3 trials (M/2730/0010, M/2730/0019 and M/2730/0022, below referred to as 10, 19 and 22). One trial was conducted where pramipexole and bromocriptine were compared with placebo in the treatment of advanced PD (M/2730/0036). In addition, 2 trials in patients with early PD (M/2730/0001 and M/2730/0004; below referred to as 01 and 04) were conducted. All trials were double blind and placebo controlled, and was conducted according to GCP rules.

Patient population

Patients of both sexes, who were at least 30 years old (mean age was 59-63 years) and had the diagnosis idiopathic PD, participated in the trials. Early disease was defined as < 7 years duration and characterised as stage I-III on the Modified Hoehn and Yahr scale, while advanced disease was characterised as stage II-IV on the same scale. Advanced disease patients were taking L-dopa/DDI (i.e. carbidopa or benserazide) and showing end-of-dose phenomena. In early disease patients, any L-dopa therapy should have been terminated at least 60 days prior to the start of the trial. Concomitant administration of selegiline or anticholinergics was allowed in both patient groups. Exclusion criteria included atypical drug-induced parkinsonian symptoms, metabolic disorders, a number of central nervous system disorders, cardiovascular disease. The number of Intention to Treat (ITT) patients in each trial is displayed in Table 1.

Table 1 Overview of the patient disposition in the main pramipexole trials

Trial	No. (%) of ITT patients		No. (%) of patients discontinuing	
	pramipexole	placebo	pramipexole	placebo
Advanced PD				
10	181 (100)	177 (99)	30 (17)	38 (22)
19	33 (100)	43 (100)	5 (15)	7 (16)
22	34 (100)	33 (100)	4 (12)	3 (9)
Early PD				
01	163 (99)	170 (99)	28 (17)	34 (20)
04	212 (99.5) [1.1mg: 54, 2.2mg: 50, 3.3mg: 54, 4.6mg: 54]	51 (100)	25 (12)	1 (2)

Dose regimens

In each study, an increasing dose phase of 6-7 weeks (12 weeks in trial 36) was allowed before the maintenance phase of 4 weeks (trials 04, 19 and 22) or 24 weeks (trials 01, 10 and 36). In all trials but 04, a flexible maintenance dose ranging from 0.26-3.3 mg/day, was given according to the tolerability of each patient. In study 04, subjects were randomised to fixed doses of 1.1, 2.2, 3.3 or 4.6 mg/day. In trial 36, the bromocriptine dose ranged from 1.25-30 mg/d given t.i.d.

Efficacy parameters

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS) was used as the primary efficacy measure, with the primary endpoint defined as the change in UPDRS scores from baseline to the last visit during the maintenance phase. The main endpoints were the UPDRS Part II, aimed at measuring activities of daily living (ADL), and Part III, which is based on clinical motor examination. Parts I-IV of the UPDRS were not used consistently in the different main trials, but endpoints were predefined and this inconsistency was therefore accepted. A number of secondary endpoints were also assessed, e.g. UPDRS parts I-III individual components, summary of modified Hoehn and Yahr scale, reduction of L-dopa dose.

Trials in advanced PD

M/2730/0010 was a US/Canadian phase III trial. Altogether 360 PD patients (181 on pramipexole, 179 on placebo) with a mean disease duration of > 9 years, showing end-of-dose phenomena when receiving a stable dose of L-dopa/DDI were included. The primary efficacy measures were UPDRS part II, assessed during 'off' and 'on' periods, and part III, assessed only during 'on' periods. From

week 3 of the maintenance phase and onwards, part II scores were significantly improved in the pramipexole group vs. placebo, with a better effect during 'off' time. Effects on part III scores were less clear, but significant improvement was demonstrated. These results were considered also to be clinically significant. A secondary endpoint of clinical relevance was the percent of 'off' time during daily waking hours. This parameter was reduced by pramipexole treatment, from 37% to 24%, corresponding to about 2.1 h, vs. 37% to 34% in the placebo group.

M/2730/0019 and **M/2730/0022** were supportive phase II trials conducted in Europe. Advanced idiopathic PD patients showing disturbances on optimized L-dopa/DDI therapy were included. In these trials, the L-dopa dose was half of that in the US/Canadian trial (400 mg vs. 800 mg daily). The primary efficacy measure, the total UPDRS score, was significantly improved in the pramipexole groups in both studies. However, in study 22, the part III score did not differ from the placebo group. These studies support a dopaminergic effect of pramipexole.

Comparative trial in advanced PD

M/2730/0036 was a phase III European/Canadian trial, comparing pramipexole (n=80), bromocriptine (n=84) and placebo (n=83) in advanced idiopathic PD patients showing disturbances on optimized L-dopa/DDI therapy. In this trial, pramipexole and bromocriptine were superior to placebo. Although the trial was not designed to specifically evaluate pramipexole versus bromocriptine, the data indicated that the drugs had comparable potency in the treatment of advanced PD.

Trials in early PD

M/2730/0001 was a US phase III trial where 335 patients were randomized to pramipexole or placebo. The 24 week maintenance phase was completed by 136 and 137 patients in each group. Patients on pramipexole showed statistically significant decreases in UPDRS II and III scores compared to the placebo group. The mean change of the UPDRS III score from baseline to week 24 was -5 vs. +0.8 in the placebo group, a change which was regarded to be also clinically significant. The changes were evident at the start and throughout the maintenance period.

M/2730/0004 was a US/Canadian phase III trial in which altogether 264 patients were randomised to fixed doses of 1.1, 2.2, 3.3 or 4.6 mg/day pramipexole or placebo. The sum UPDRS I-III score was used as the primary efficacy variable. Based on that measure, all pramipexole doses showed a similar therapeutic efficacy, which was superior to that of placebo, thus no dose-effect relationship was demonstrated. UPDRS III scores were also significantly different but no significant differences were demonstrated for UPDRS II scores.

Summary and conclusions on efficacy

Overall, the clinical program for pramipexole was well conducted. The patients studied were representative of the target population with respect to concomitant therapies and other demographic variables. In general, the endpoints chosen to assess efficacy were regarded as clinically relevant.

At clinical use, doses of pramipexole like other DA agonists, are titrated to achieve an individual optimal therapeutic response. The minimum daily effective dose has not been defined, but 1.1 mg/d was found to be the lowest dose with a clear effect vs. placebo. Although no dose-effect relationship was demonstrated in trial 04 (similar effects were seen with all doses used ranging from 1.1 to 4.6 mg/d), individual patients may need doses higher than 1.1 mg to gain a sufficient effect. Overall, the proposed dosage was supported by the clinical results, and the proposed method for dose titration is in line with clinical practice for most antiparkinsonian drugs. Thus, the dosage recommendations including a maximum daily dose of 3.3 mg, given in 3 divided doses, as outlined in the SPC are regarded as adequate.

In advanced idiopathic PD patients showing end-of-dose phenomena on optimized L-dopa/DDI (i.e. carbidopa or benserazide) therapy, a clinically relevant and statistically significant effect of pramipexole has been demonstrated for up to 6 months in comparison to placebo. In this patient population, one comparative trial indicated a similar effect of pramipexole and bromocriptine which both were superior to placebo.

With respect to treatment of early disease patients, i.e. patients not receiving L-dopa therapy, the available data are not sufficient to support this indication. Although pramipexole showed statistically significant effects in comparison to placebo, the lack of comparison with other antiparkinson treatment

was regarded as a major deficiency. Furthermore, the long-term efficacy in this population was not sufficiently proven.

Clinical safety

The safety data (cut-off date February 1996) for pramipexole were primarily derived from 10 controlled and completed trials (i.e. the 6 trials described in the efficacy section and 4 trials not included in the efficacy analysis due to poor patients recruitment or single blind design), comprising altogether 782 pramipexole-exposed patients, 633 patients on placebo and 84 patients on bromocriptine. Additional data on deaths, serious adverse events and discontinuations were obtained from 6 open-label trials and from trials in schizophrenia (deaths only). In these trials the total number of patients exposed to pramipexole was 1511 of which more than 800 were treated for at least 1 year.

The total number of deaths reported for pramipexole and placebo was 14 and 3, respectively, of which 12 (0.7%) and 2 (0.4%) occurred in the completed studies. When corrected for the longer exposure time to pramipexole due to the non-controlled open-label phase, the death incidence was considered comparable for pramipexole and placebo. In one occasion, the observer reported a possible relation to treatment.

In clinical trials, abnormal vision was reported in 3% of pramipexole patients vs. 0.4% in the placebo group. Furthermore, preclinical data showed that pramipexole induced retinal degeneration in albino rats. Detailed ophthalmological investigations have only been performed in a limited number of patients receiving pramipexole. However, the available data are not sufficient to conclude that pramipexole does not cause retinal degeneration. Therefore, ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities should occur. In addition, effects of pramipexole on ocular function will be monitored in a post marketing study.

There were also indications of increased dyskinesia in patients administered pramipexole and concomitant L-dopa therapy, particularly during the initial pramipexole dose titration, and that the incidence of dyskinesia was higher in women. This may, at least partly, be related to the increased rate of L-dopa absorption induced by pramipexole (see section on Pharmacokinetics above). In cases of increased dyskinesia, the L-dopa dose should be reduced. In addition, a post marketing interaction study with pramipexole and L-dopa will be conducted to further evaluate gender differences.

In the following sections, data from the 10 completed controlled trials are presented. Treatment was discontinued in 15%, 20% and 20% of patients treated with pramipexole, placebo and bromocriptine, respectively. In the pramipexole treated patients, the most common reasons for discontinuation were hallucination (2.7% vs. 0.4% for placebo), nausea (1.4% vs. 0.7% for placebo), hypotension (1% vs. 0.5% for placebo) and somnolence (1.3% vs. 0.2% for placebo) and in the placebo group extrapyramidal symptoms (5.5% vs. 1.4% for pramipexole) and 'no drug effect' (1.3% vs. 0.1% for pramipexole).

Most adverse events occurred with similar frequencies in the pramipexole and placebo groups; CNS-related effects being most common. In the pramipexole group, the incidences of hallucinations (13% vs. 5% placebo) and somnolence (15% vs. 6% placebo) were increased while extrapyramidal symptoms were more frequent in placebo treated patients (20% vs. 14% pramipexole). Nausea and constipation were also more frequent in the pramipexole group. Both gastrointestinal and CNS side effects were more frequent during the initial dose ascending phases of the trials. However, hallucinations, somnolence and insomnia did not diminish over time. When comparing patients with early and advanced disease, hallucinations were most common in advanced disease patients while somnolence occurred more commonly in early disease patients. In the comparative trial, the side effect profiles for pramipexole and bromocriptine were in general similar.

Long-term safety of pramipexole has not been assessed in placebo-controlled trials. However, more than 500 patients have been exposed to 2.2-3.3 mg/d of pramipexole for more than 60 weeks in open studies. There were no indications of new side effects or of an increased frequency of already known adverse effects. Thus, the available data are considered to provide acceptable evidence for long-term safety of pramipexole.

Sudden onset of sleep during daily activities has been reported in rare cases post marketing. This can be life threatening to the patient or others depending on the circumstances. These episodes have been reported in some cases without awareness of warning signs. If this occurs, reduction of dosage or

termination of therapy should be considered. Patients being treated with pramipexole must be informed not to drive or engage in other activities where impaired alertness could put them or others at risk of serious injury or death (e.g. operating machines). Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole.

Summary and conclusions on clinical safety

The side-effect profile of pramipexole includes hallucinations, sleep disturbances and gastrointestinal effects. In addition, there were concerns regarding the potential of pramipexole to cause ocular toxicity, including retinal degeneration. Since there are not sufficient data available to conclude that pramipexole does not cause retinal degeneration, ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities should occur. There were also concerns regarding a possible increased dyskinesia frequency, particularly in women. This may be related to an interaction between pramipexole and L-dopa resulting in an increased L-dopa absorption rate. In cases of increased dyskinesia, the L-dopa dose should be reduced. By these precautions, which are pointed out in the SPC, the potential safety concerns (ocular toxicity and the L-dopa interaction) were regarded to be adequately addressed.

Overall risk/benefit analysis

In advanced idiopathic PD patients showing end-of-dose phenomena on optimized L-dopa/DDI (i.e. carbidopa or benserazide) therapy, a clinically relevant and statistically significant effect of pramipexole has been demonstrated for up to 6 months in comparison to placebo. In this patient population, one comparative trial indicated a similar effect of pramipexole and bromocriptine which both were superior to placebo.

The side-effect profile of pramipexole includes hallucinations, sleep disturbances and gastrointestinal effects. Based on findings in long-term toxicity studies in albino rats, which indicated dose-related retinal degeneration, there were concerns regarding the potential ocular toxicity. The available clinical data are not sufficient to conclude that pramipexole does not cause retinal degeneration. There was also a concern regarding a possible gender difference in dyskinesia frequency, which may be related to the increased rate of L-dopa absorption. Recommendations regarding ophthalmologic monitoring and L-dopa dose adjustments have been included in the SPC. By these precautions, the potential safety concerns were considered to be adequately addressed.

Taken together, the overall risk / benefit ratio for pramipexole was considered to be positive for the following indication: Sifrol tablets are indicated for treatment of signs and symptoms of advanced idiopathic Parkinson's disease in combination with levodopa i.e. over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations).

5. Conclusion

Sifrol is presented as tablets containing pramipexole dihydrochloride monohydrate. There are 5 tablet strengths containing 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, and 1.1 mg of the active substance pramipexole, respectively corresponding to 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, and 1.5 mg of pramipexole dihydrochloride monohydrate.

Overall, an acceptable quality of the product has been demonstrated in the chemical, pharmaceutical documentation.

Based on preclinical pharmacodynamic studies, pramipexole has been shown to be a selective and specific full DA agonist with high affinity for the DA D2 receptor family, and particularly the D₃ receptor subtype.

In advanced idiopathic PD patients showing end-of-dose phenomena on optimized L-dopa therapy, a clinically relevant and statistically significant effect of pramipexole has been demonstrated. The safety concerns, potential ocular toxicity and gender differences with respect to dyskinesia have been adequately addressed. Therefore, the CPMP considered the risk / benefit ratio being positive and recommended the granting of a Marketing Authorisation for all strengths and presentations of this medicinal product.