EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Sifrol / Mirapexin

(pramipexole)

Procedure No. EMEA/H/C/000133/P46 040
Procedure No. EMEA/H/C/000134/P46 038

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1 Introduction

Paediatric Investigation Plans (PIP) for Sifrol and Mirapexin, pramipexole dihydrochloride monohydrate, were agreed by EMA on 12 September 2008. The conditions are combined vocal and multiple motor tic disorder (de la Tourette) and Restless Legs Syndrome (RLS). The granted waiver applies to preterm newborn infants, term newborn infants, infants and toddlers and children less than 6 years for both conditions.
A deferral has been granted for the paediatric RLS study. The paediatric Committee (PCDO) had agreed that safety results from the paediatric Tourette's Disorder development program and a positive risk benefit assessment for the potential lifetime dopaminergic treatment of RLS starting at childhood ages, should be available prior to starting the paediatric RLS study.
The Marketing Authorisation Holder (MAH) also agreed to conduct a 30-week toxicity study in juvenile Rhesus monkeys as a follow-up measure.

This report covers the following post-authorisation commitments undertaken by the MAH:

Paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH submitted:

- The Final Report for clinical trial 248.642 titled:

"An open-label, flexible dose. follow-up study to evaluate safety and efficacy of oral pramipexole (0.0625-0.5 mg/day) for 24 weeks in children and adolescents (age 6-17 years) diagnosed with Tourette Syndrome according to DSM-IV criteria and who have completed the double-blind phase of either study 248.641 or 248.644".

and,

- The Final Report for the non-clinical study U09-1156 titled:

"Pramipexole: Thirty-week toxicity study in juvenile Rhesus monkeys followed by a twelve-week recovery period: use of nonhuman primate model for studying the consequences of long-term dopaminergic receptor stimulation on complex brain functions using the NCTR operant battery".

2 Assessment

2.1 Report for clinical trial 248.642

Tourette's Disorder
Tourette's Disorder is a neuropsychiatric disorder that is characterized by childhood onset of motor and phonic tics. A dopaminergic hyperfunction in certain brain areas in Tourette's Disorder would explain why postsynaptic dopamine antagonists such as antipsychotics as well as dopamine agonists with a presynaptic component may be effective in suppressing tics associated with Tourette's Disorder.

From epidemiological studies it seems likely that the prevalence of Tourette's Disorder in the general population ranges from 4.3 to 10 per 10,000.

The main characteristics of Tourette's Disorder appear to be independent of culture and, in general, symptoms are similar worldwide. Tourette's Disorder is found in all countries, all racial groups and is three to four times more common in males.

The age range for this paediatric development program was 6-17 years, inclusive. This age range is based on published data showing that onset of tics associated with Tourette's Disorder generally occurs at the age of 6 years, with tics progressively worsening and showing the greatest severity at 10 years.

Clinical program as agreed in the PIP

The following clinical studies in patients with Tourette's Disorder were planned in line with the approved PIP:

Study 248.644, a randomised, double-blind, placebo-controlled, flexible dose study to evaluate efficacy and safety of pramipexole immediate release (IR) (0.0625-0.5 mg/day) vs. placebo for 6 weeks in children and adolescents (age 6-17 inclusive) diagnosed with Tourette's Disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria.

Study 248.642, an open-label, flexible dose study to evaluate efficacy and safety of pramipexole IR (0.0625-0.5 mg/day) for 24 weeks in children and adolescents (age 6-17 inclusive) diagnosed with Tourette's Disorder according to DSM IV criteria in those patients who have completed the double-blind phase of either Study 248.644 or 248.641.

Study 248.641, a Phase III, double-blind, placebo-controlled, 12-week fixed dose trial with pramipexole 0.125-0.5 mg/day per os to investigate efficacy, safety, and tolerability and safety in children and adolescents (age 6-17 inclusive) diagnosed with Tourette's Disorder according to DSM IV criteria.

The clinical trial report for study 248.644 was submitted in January 2010. Study 248.642 was prematurely terminated as the negative results of study 248.644 had become available. It should be noted that prior to the initiation of Study 248.641, the program was cancelled, so all patients in this study had completed the 248.644 study. The clinical trial report is being submitted along with this critical expert overview. The planned Phase III study 248.641 will not commence due to the negative results of Study 248.644 and the termination of the paediatric Tourette's program.

Assessment comments:

The clinical trial report for study 248.644 was submitted and assessed as part of a type II variation (Sifrol II/56 and Mirapexin II/64).

In May 2010 CHMP agreed that the results of study 248.644 didn't indicate any efficacy of prapmipexole in Tourette Disorder and consequently the termination of the Tourette's development programme was considered acceptable.

In addition the negative efficacy (and safety) results of this study were included in section 5.1 of the SmPC by this variation.

Conclusions for open-label study 248.642

This study was important for the long-term evaluation of the safety and efficacy of pramipexole in the treatment of Tourette's Disorder. The open-label trial design was appropriate for an extension study of patients who completed one of the double-blind trials (either 248.644 or 248.641). The study evaluated the safety and efficacy of pramipexole over a 24-week period in children and adolescents diagnosed with Tourette's Disorder.

It was anticipated that 120 patients would be entered into the trial (this is approximately 60% of the total number of patients expected to have entered trials 248.641 and 248.644). Due to the early termination of the trial, a total of only 45 patients received at least one dose of study medication. The mean exposure to treatment was 128.1 days. The range of exposure was 22-184 days.

As this trial was discontinued prematurely, enrolment was significantly less than what was planned (120 planned entered vs. 45 actual entered) and a high number of patients (23 of 45, 51.1%) were prematurely discontinued. Therefore, the objectives of this study could not be fully assessed.

Assessment comments:

In accordance with the assessment of study 248.644, the CHMP considerd the above discussion and conclusion of the MAH acceptable.

2.2 Report for the non-clinical study U09-1156

Table 1. Results from the juvenile repeat-dose toxicity studies conducted with pramipexole.

Study ID GLP status	Species (age at dosing) /Sex/ Number/ Group	Dose/Route/Duration	NOAEL (mg/kg/day)	Major findings
Boi0340060108 (u07-1740) non-GLP Dose Finding	SD Rat (21 days)/ 8/sex/group (TOX) 6-16/sex/group (TK)	0.5, 4, 20 mg/kg/day PO 4-weeks	ND	**≥0.5:** **Clinical signs:** Over-/underactive behaviour, partially closed/closed eyelids, ↓ Bodyweight gain **≥4:** **Clinical signs:** Piloerection, abnormal gait, ↓ food consumption **Organ weight:** ↓ Seminal vesicles (absolute) **Sexual maturation:** Delay in vaginal opening **25:** **Clinical signs:** ↑ Vocalisation upon handling **Organ weight:** liver (♂), pituita **Sexual maturation:** Slight delay in preputial separation
Boi0349072057 (u072124) GLP	SD Rat (21 days)/ 18-20/sex/group	0.5, 4, 20 mg/kg/day PO 7-weeks with 5-weeks recovery	ND	**F_0:** **≥0.5:** **Clinical signs etc.:** ↓ Bodyweight gain **Haematology:** ↓ RBC (♀) **Clinical chemistry:** ↑ urea (♂),↓ total protein (♀), albumin (♀), globulin (♀) **Organ weights:** ↑ ovarian, **Histopathology:** ↑ corpora lutea **Sexual maturation:** Delay in vaginal opening **≥4:** **Clinical signs etc.:** ↓ food consumption, low habituation to auditory startle, reduced performance in the Morris maze **Haematology:** ↓ haemoglobin (♀), extended prothrombin clotting times (♀) **Clinical chemistry:** ↓ oestradiol (♀), prolactin, slight ↑ ASAT (1.2x at max), slight ↑ ALAT (1.4x at max), ↑ alkaline phosphatase activities (1.3x at max), ↑ urea (1.4x at max), ↓ glucose (♂),↓ cholesterol (♀), total protein, ↓ globulin (♀) **Organ weights:** ↓ pituitary (♀), thymus (♀) **F_1 litter responses:** ↓ implantation sites, ↓ total and live litter size

Study ID GLP status	Species (age at dosing) /Sex/ Number/ Group	Dose/Route/Duration	NOAEL (mg/kg/day)	Major findings
				20: **Clinical signs etc.:** ↓ Bodyweight, ↑ ambulatory and rearing activity (♀), hyperactive **Haematology:** ↓ haematocrit, ↓ haemoglobin, ↓ RBC, ↓ platelet (♀), activated partial thromboplastin time (♂) **Clinical chemistry:** ↓ triglyceride, ↓ calcium, (♂),↓ total protein, ↓ albumin, ↓ globulin **Organ weights:** ↓ pituitary, ↓ relative adrenal **Histopathology:** ↓ prolactin positive cells in the pituitary (only dose lvl tested) **≥0.5 (recovery):** **Clinical chemistry:** ↓ albumin (♀) **20 (recovery):** **Clinical signs etc.:** ↑ Bodyweight gain, ↑ ambulatory and rearing activity (♀) **Clinical chemistry:** ↑ alkaline phosphatase activities
Sbl177 (u061760) GLP	Rhesus monkeys (14-16 months) 3/sex/group (main) 2/sex/group (recovery – only control and HD)	0.1, 0.3, 1 mg/kg/day PO 4-weeks with 2-week recovery	0.1 mg/kg/day ($C_{2\ hour}$=14 ng/mL)	**≥0.3:** **Clinical signs etc.:** ↑ heart rate without effect on BP and ECG **Clinical chemistry:** ↓ prolactin **Histopathology:** slight cortical atrophy of the thymus (adrenals (♀) **Organ weights:** ↓ thymus, **1:** **Clinical signs etc.:** Somnolence, incomplete eyelid, ↑ spontaneous activity **Clinical chemistry:** ↓ phospholipids (♀), slight ↑ ASAT, slight ↑ ALAT, **Haematology:** ↑ WBC (incl. eosinophils, basophils, neutropils,, monocytes, lymphocytes) **1 (recovery):** **Clinical chemistry:** ↓ phospholipids (♀) **Histopathology:** slight cortical atrophy of the thymus (♂),
E0725201 (u091156)	Rhesus monkeys (20-24	0.1, 0.5, 2 mg/kg/day PO	0.5 mg/kg/day	**≥0.1:** **Clinical signs etc.:** Higher behavioural training scores (mainly

Study ID GLP status	Species (age at dosing) /Sex/ Number/ Group	Dose/Route/Duration	NOAEL (mg/kg/day)	Major findings
GLP	months) 4/sex/group	30-weeks with a 12-week recovery	(C_{max}=110 ng/mL, AUC=568 ng.h/mL)	in home-cage behaviour (mainly ♂ learning task performance (mainly ♂) **Clinical chemistry:** ↓ prolactin **≥0.5:** 3 unscheduled deaths (assigned to viral infections in the CNS) **Clinical signs etc.:** ↓ BP and ↓ heart rate without any effects on the ECG **Haematology:** ↓ lymphocytes, ↑ neutrophils, **Clinical chemistry:** ↓ alkaline phosphatase **2:** **Clinical signs etc.:** lower behavioural training scores, lower learning task performance (mainly ♀) **Haematology:** ↓ platelet **Clinical chemistry:** ↓ triglyceride **≥0.5: (recovery):** **Clinical signs etc.:** ↑ heart rate **Haematology:** ↓ haematocrit, ↓ haemoglobin, **Clinical chemistry:** ↓ alkaline phosphatase**,** ↑ prolactin, ↓ estradiol **2 (recovery):** **Histopathology:** Acute focal minimal hepatocellular necrosis

HD – High dose group

SD – Sprague Dawley

Administration of pramipexole resulted mainly in functional effects, mainly involving the CNS in both rats and Rhesus monkeys and the female reproductive system in the rat. Both effects are considered to result from an exaggerated pharmacodynamic effect of pramipexole. In rats (including juvenile) as well as Rhesus monkeys (including juvenile), clinical signs observed included somnolence, underactive as well as overactive behaviour and changes in motor or spontaneous activity. In the juvenile rat, the effects at the end of the treatment period on learning and memory at 4 or 20 mg/kg/day were considered to be related to the changes in behaviour with regards to activity that were seen in association with treatment and were not present anymore at the end of recovery. Also, in the juvenile rat, motor activity was only affected at the very high dose of 20 mg/kg/day. No clinically relevant effects of pramipexole were observed in the study on fertility and early embryonic development or in the study on pre- and postnatal development in rats. Results of the studies on embryo-fetal development in rats and rabbits did not indicate a compound-induced teratogenic effect. Embryo/fetotoxicity was found in the rat at maternotoxic doses. In the juvenile rat, oestrous cycles, mating performance and fertility, offspring survival and development were not affected at any dose. The NOEL for reproductive performance was 0.5 mg/kg/day. With respect to the known class effects of dopaminergic agents, the NOAEL for prolactin levels and effects on the ovaries was 0.5 mg/kg/day in

the juvenile rat. It should be noted that the role of prolactin in rodents with regard to hormonal regulation and affected organs is different than that in humans: in the rat, prolactin doubles as the luteotrophic hormone while in humans this function is assumed by luteinising hormone. Therefore, the above described findings in the rat are considered to be species-specific and of no biological relevance for the human situation. However, given the different physiological function in man, prolactin deficiency or hypoprolactinemia is not accompanied by severe side effects and therefore is not treated in clinical practice. In addition, decreased prolactin levels in the study in juvenile Rhesus monkeys at the higher doses had not induced any adverse effects on any of the hormones tested.
A special focus for a dopamine agonist with regard to development is CNS. Special neuropathology was performed in the juvenile rat and juvenile monkey study. The NOAEL for neuropathology in the juvenile rat was 20 mg/kg/day, in the juvenile monkey 2 mg/kg/day.
PK data in paediatric RLS patients are available (U08-3440). Exposure multiples for the proposed highest total daily dose of pramipexole in the clinical Tourette Syndrome program were estimated taking into account the PK results of Study 248.600 (U08-3440) and the plasma levels at the NOAEL (0.5 mg/kg/day) from the 30-week study in juvenile Rhesus monkeys. In addition, the following assumptions were used a) the PK properties of pramipexole in paediatric Tourette Syndrome patients will not differ from that in RLS patients at the same age range; b) the body weight of at least 20 kg for a paediatric patient (at an age of six years); c) it had been planned that the maximum exposure in the proposed phase III study should not exceed 0.5 mg/day as the daily and 0.25 mg as a single dose (the daily dose of 0.5 mg/patient is equivalent to 0.025 mg/kg at a body weight of 20 kg). Based on these facts, the dose multiples for the maximum intended clinical dose in paediatric patients are ~80 based on C(max) and ~20 based on AUC. These exposure multiples were considered sufficient for the use of pramipexole in paediatric patients aged 6 years and older.

Assessment comments:
Pharmacodyamic effects on brain functions were observed in rats and monkeys without any histopathological changes. The dose-response seemed to be bell-shaped. Based on the monkey toxicity data alone, the safety margins are sufficient for the proposed daily dose to children. However, rat toxicity data raises a concern regarding the reproduction performance and sexual maturation. The effects consisted of low plasma levels of oestradiol and prolactin (the latter also observed in monkeys), marked delay in vaginal opening and bodyweights on completion of opening, slight delay in preputial separation and bodyweight at completion, low number of implantation sites, and low number of total and live litter size. The safety margin for the effects on reproduction performance seems to be sufficient (AUC > 1000 ng.h/mL at the NOAEL of 4 mg/kg for low number of implantation sites, total and live litter size). The MAH assumed that the effect on preputial separation is attributed to a delay in physical rather than sexual maturation due to the low body weight gain during dosing. However, the effect may be related to the effects on prolactin and vaginal opening. The MAH has suggested that the effects on prolactin (and ovarian weights) may be due to a species-specific effect of dopamine agonists on hormone secretion. It is acknowledged that the delay of preputial separation and vaginal opening may be due to a hormonal disturbance. However, a NOAEL could not be established with regards to the delay in vaginal opening. The relevance of the effects on prolactin, oestradiol, and male and female maturation for the sexual development in human children dosed with pramipexole is not known. For these reasons, the CHMP concluded that the following statement should be included in section 5.3 of the SmPC, e.g., “A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.”

3 Overall Conclusion And further action required

P46 040/P46 038

Overall Conclusion:

As outcome of this assessment, the CHMP requested that the MAH should update the Product Information as follows and to submit the corresponding variation within 2 months:
In section 5.3 of the SPC should be stated, e.g., “A delay in sexual development (i.e. preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.”