EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Evaluation of Medicines for Human Use

CHMP assessment report

Sifrol

International Nonproprietary Name: pramipexole

Procedure No. EMEA/H/C/000133/X/0054

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 22 October 2009 an application for Marketing Authorisation to the European Medicines Agency for Sifrol 1.57 mg and 2.62 mg prolonged-release tablets, pursuant to Annex II, point 2 iii of the Commission Regulation (EC) No 1085/2003.

Boehringer Ingelheim International GmbH is the Marketing Authorisation Holder for Sifrol 0.088 mg 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets authorised on 14 October 1997 under part Part b of the Annex to Council Regulation No. (EEC) 2309/93 of 22 July 1993, as amended and 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg prolonged-release tablets authorised on 8 October 2009 pursuant to Annex II, point 2 iii and iv of the Comission Regulation (EC) No 1085/2003.

Information on paediatric requirements

Not applicable.

The Rapporteur appointed by the CHMP was **Jens Ersbøll.**

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 22 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 February 2010.
- During the meeting on 15-18 March 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sifrol on 18 March 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 March 2010.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Pramipexole is a nonergot dopamine agonist with full intrinsic activity. It shows high selectivity for interacting with receptors of the D2 subfamily, which consists of D2, D3 and D4 receptors. Pramipexole exhibits higher affinity for the D3 receptor subtypes than for D2 or D4 subtypes.

Pramipexole immediate release tablets have been authorized in the EU and USA since 1997. Immediate release tablets are indicated for the treatment of signs and symptoms of either early Parkinson's disease or advanced Parkinson's disease in combination with levodopa as well as for Restless Legs Syndrome. The immediate release tablets in Parkinson's disease have to be taken 3 times a day.

Boehringer Ingelheim has developed prolonged-release tablets containing pramipexole that can be administered once daily. This alternative formulation is beneficial to patients with Parkinson's disease as this new pharmaceutical form will allow patients to treat their symptoms with a single daily dose, thereby increasing patient convenience and compliance. In addition, administration of the prolonged-release tablets results in a pharmacokinetic profile with less pronounced maximal plasma levels and more stable plasma levels over time. The prolonged-release tablets were approved on 8 October 2009 pursuant to Annex II, point 2 iii and iv of the Comission Regulation (EC) No 1085/2003 (line extension application).

This application was submitted under Article 8(3) of Directive 2001/83/EC as an extension to the marketing authorization for Sifrol 0.088 mg 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets and 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg prolonged-release tablets (EU/1/97/050/001 - 027) marketed by Boehringer Ingelheim International GmbH to add new strengths 1.57 mg and 2.62 mg of prolonged-release tablets.

2.2. Quality aspects

Introduction

Additional strengths of Sifrol are presented as prolonged-release tablets containing 1.57 mg or 2.62 mg of pramipexole (active substance) as the pramipexole dihydrochloride monohydrate salt. Excipients used in the preparation of prolonged-release tablets are well known excipients used in tablets preparations such as hypromellose, maize starch, carbomer 941, colloidal anhydrous silica and magnesium stearate.

Tablets are white to off-white of oval shape and have a code embossed (one side with the code P12 (1.57 mg) or P13 (2.62 mg) and one side with the Boehringer Ingelheim company symbol.

Sifrol prolonged-release tablets is packed in polyamide/aluminium/PVC blisters. Each blister strip contains 10 prolonged-release tablets. Cartons containing 1, 3 or 10 blister strips (10, 30 or 100 prolonged-release tablets).

Active substance

The active substance used in this formulation is identical with the one used in the manufacture of the approved Sifrol presentations (EU/1/97/050/001 - 027).

Medicinal Product

- ***Pharmaceutical Development***

The objective of the development was to develop two additional strengths of prolonged-release tablets based on the currently approved formulations and to achieve similar *in-vitro* dissolution profiles. The formulations for the new strengths are comparable with the currently approved formulations.

The proposed formulation is a matrix single-unit prolonged-release tablet with pramipexole dihydrochloride monohydrate dispersed homogeneously throughout the matrix. Additional strengths have been developed based on the same formulation principle. The release mechanism of the active substance from the matrix is by diffusion and erosion mechanism. The active substance is dispersed homogeneously in the tablet matrix. By the diffusion mechanism, gastro-intestinal fluids penetrate the insoluble matrix and diffuse back out together with dissolved drug. By the erosion mechanism, parts of the matrix surface separate from the core and the drug is directly exposed to the gastro-intestinal fluids. The *in-vitro* release characteristics of the active substance from the tablets are proportional to the square-root of time.

Comparative in-vitro dissolution profiles showing similarity between the approved strengths and the strengths applied for were presented. Based on guideline requirements and the *in-vivo in-vitro* correlation (IVIVC) established during the approval of the 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg prolonged-release tablets, a justification was provided for not performing bio-equivalence studies on the new prolonged-release strengths applied for. The biowaiver concept could be applied because safety and efficacy was considered proven based on Phase III studies, where the dosage strengths 1.5 + 0.75 mg and 3.0 + 0.75 mg were used to achieve the intermediate dose strengths applied for.

In addition bioequivalence studies were not needed, as in line with the NfG on *modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation, CPMP/EWP/280/96 Corr)*, which refers to the criteria described in the current BA/BE guidance (*NfG on the investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98*, Section 5.4, the same composition, design and operating principle of equipment and the same general manufacturing process has been utilized for all seven strengths throughout pharmaceutical development at the development site and also for manufacturing of the primary stability batches and phase III clinical trial batches at the production site. The production site is the intended commercial manufacturing site. No changes were implemented for the manufacturing process of pramipexole dihydrochloride monohydrate used in phase III clinical studies compared to the primary stability batches as well as to the intended commercial manufacturing process at the manufacturing site.

The primary packaging for additional strengths is the same as for already authorised strengths of prolonged-release tablets, which is polyamide/aluminium/PVC blisters

- ***Adventitious Agents***

None of the excipients present in the formulation are of animal or human origin. Magnesium stearate used in the manufacturing process of the medicinal product is of vegetable origin.

- ***Manufacture of the Product***

The manufacturing process of the drug product comprises two main steps, i.e. dry-blending with a diffusion mixer and subsequent compression into tablets using a power assisted tablet press. The compressed tablets are packed in blisters in folded cardboard box.

Standard in-process controls are routinely performed during the manufacturing process to control the drug product quality. Acceptance criteria and specification limits have been set-up. The proposed in-process control tests are adequate to control the critical steps of the manufacturing process.

Prospective validation of the manufacturing process has been carried out with three production scale batches of each strength. The validation batches have been manufactured by the proposed commercial process. Acceptable validation results have been presented, demonstrating a robust process leading to a product complying with the set acceptance criteria. A homogenous distribution of the active substance in the blend was confirmed by the data presented. It has been proven that segregation/deblending do not occur during the compression of tablets. Stratified assay and assay values are well within limits. The dissolution rate of the individual tablets all comply with the proposed criteria. Dissolution results for all strengths are all within the set limits.

- ***Product Specification***

The product specification is a standard one for tablets and contains tests with suitable limits for appearance, identification (HPLC and UV), assay (HPLC), loss on drying, dissolution, uniformity of dosage units (HPLC) and degradation products (HPLC).

Full details of all analytical methods have been provided. All chromatographic procedures have been appropriately validated. Validations comply with the ICH harmonised Tripartite Guideline Q2(R1) Validation of Analytical Procedures: Text and Methodology. A summary of the validation results for the key methods: identification, dissolution, degradation, assay, and content uniformity have been provided.

The HPLC method for dissolution has been validated for specificity, linearity in the range, accuracy, repeatability and intermediate precision. Robustness in terms of filter validation and stability of sample and standard preparation has been investigated.

The HPLC method for degradation products has been validated with respect to the active, specified impurities and unspecified impurities for specificity/selectivity, accuracy, precision (repeatability and intermediate precision), linearity, range, limit of quantification, robustness and stability of solutions. Limit of quantitation and limit of detection have been determined.

The HPLC methods for assay and content uniformity have been validated with respect to specificity/selectivity, accuracy, precision (intermediate precision only), linearity, range, robustness and stability of solutions.

Batch analysis results have been provided for 8 batches, including development, validation and stability batches. The batches have been tested for compliance with the specifications in place at the time of testing. All results comply with the specification valid at the time of the testing. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. The batch analysis data showed that prolonged-release tablets can be manufactured reproducibly according to the agreed finished product specification.

- ***Stability of the Product***

The same shelf-life and storage conditions were proposed as for already approved strengths. 3 batches (commercial scale) of each strength were included in the stability study and tested according to ICH requirements and 6 months of comparative stability data were presented. No extrapolation has been made because of the limited data available. The tablets used in the primary stability study are identical to the proposed commercial product. They were manufactured according to the proposed commercial process and packaged in the proposed market packaging materials.

Test methods used in “Stability studies” are the same as the one used at release except the test for identification and uniformity of dosage units, which are performed only at release.

Based on the fact that the additional strengths applied for were comparable with the currently approved strengths regarding composition, manufacturing process and packaging materials and the changes seen in the presented stability study were comparable to the changes seen during stability testing of the currently approved strengths, there was no reason to expect that the stability of the dosage strengths applied for was different than the stability of the currently approved dosage strengths. The initiated stability study will be continued beyond the proposed shelf-life.

Photostability studies have been conducted in accordance with the ICH guideline Q1B on the currently approved strengths, and no significant changes were observed after directly exposure to light. Due to the close similarity of the formulations for the new and marketed strengths, the new strengths are expected to be equally photostable.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SmPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The new strengths of 1.57 mg and 2.62 mg of prolonged-release tablets have been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The results of the tests indicate that the drug product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

2.3. Non-clinical aspects

Introduction

This application is a line extension to the authorised medicinal product Sifrol. No new non-clinical pharmacological, pharmacokinetic or toxicology studies have been performed for the two additional prolonged-release formulation strengths of pramipexole.

Pharmacology

Not Applicable

Pharmacokinetics

Not Applicable

Toxicology

Not Applicable

2.4. Clinical aspects

Introduction

No new Phase I or Phase III trials have been conducted in the context of this submission for registration of the two additional dose strengths 1.57 mg and 2.62 mg pramipexole prolonged release. In the submitted dossier, the MAH summarised the efficacy and safety data for these two intermediate dose levels from the 248.524 study in early PD and the 248.525 study in advanced PD, as already submitted and assessed in procedure EMEA/H/C/133/X/51.

GCP

Not Applicable

Pharmacokinetics

Not Applicable

Pharmacodynamics

Not Applicable

Clinical efficacy

Not Applicable

Clinical safety

Not Applicable

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The MAA submitted a risk management plan.

Summary table of the risk management plan:

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Binge eating, Compulsive shopping, Pathological gambling, Hypersexuality and other Abnormal	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and	Routine risk minimisation activities. The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use):

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
behaviour	RLS studies as soon as available. PERIODIC REVIEW IN PSUR Trial 248.619 (DOMINION): cross-sectional, retrospective screening and case-control study in PD patients treated with pramipexole and other antiparkinson drugs, completed Trial 248.659: Observational RLS study, ongoing	*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 {TRADE NAME}. 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/tapered discontinuation should be considered.* *Behavioural symptoms of impulse control disorders and compulsions* are described as common, *compulsive shopping, hypersexuality, pathological gambling* as uncommon and *binge eating* as psychiatric disorders with unknown frequency in section 4.8 of the SmPC (Undesirable effects). Furthermore the following information is provided in Section 4.8 of the SmPC (Undesirable effects): *Impulse control disorders and compulsive behaviours: Patients treated with dopamine agonists for Parkinson's disease, including {TRADE NAME}, 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 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤ 65 years), not*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		being married and self-reported family history of gambling behaviours.
Suicide-related behaviour	Routine pharmacovigilance PERIODIC REVIEW IN PSUR	None
Augmentation, post treatment worsening after withdrawal and rebound in RLS patients	Routine pharmacovigilance PERIODIC REVIEW IN PSUR Trial 248.629: randomised, double-blind, placebo-controlled, dose titration trial with pramipexole to investigate the long-term efficacy, safety and tolerability in patients with RLS; completed	Routine risk minimisation activities. The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use): *Augmentation: Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of {TRADE NAME} in patients with Restless Legs Syndrome were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of {TRADE NAME} and the appropriate management of these events have not been evaluated in controlled clinical trials.*
SIADH	Routine pharmacovigilance Planned pooled analysis of controlled clinical trial data concerning SIADH PERIODIC REVIEW IN PSUR	None
Delirium/Mania	Routine pharmacovigilance Planned pooled analysis of controlled clinical trial data concerning delirium/mania PERIODIC REVIEW IN PSUR	None
Dyspnoea	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	Routine risk minimisation activities. *Dyspnoea* is described as uncommon respiratory, thoracic, and mediastinal disorders in section 4.8 of the SmPC (Undesirable effects).
Pneumonia	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available.	Routine risk minimisation activities. *Pneumonia* is described as uncommon infection in section 4.8 of the SmPC (Undesirable effects).

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	PERIODIC REVIEW IN PSUR	
Bronchitis	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	None
Cardiac failure	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use): *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*. This information is considered to reflect this issue appropriately.
Retinal degeneration	Routine pharmacovigilance Trial 248.538: randomised, parallel group, ophthalmologic safety study, ongoing	Routine risk minimisation activities. The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use): *Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur*. The following information is included in section 5.3 of the SmPC (Preclinical safety data): *[…] 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.*
Decreased appetite/Anorexia	Routine pharmacovigilance	Weight decrease is listed in section 4.8 (Undesirable effects) of the SmPC. The adverse events decreased appetite/anorexia were frequently associated with weight decrease and, thus, can be considered as medically covered by the listed side effect weight decreased.
Skin melanoma	Routine pharmacovigilance	None
Diplopia	Routine pharmacovigilance	Routine risk minimisation activities. *Visual disturbance including vision blurred and visual acuity reduced* is described as common eye disorder in section 4.8 of the SmPC

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		(Undesirable effects). Diplopia is considered as covered by this description.
Photopsia	Routine pharmacovigilance	Routine risk minimisation activities. *Visual disturbance including vision blurred and visual acuity reduced* is described as common eye disorder in section 4.8 of the SmPC (Undesirable effects). Photopsia is considered as covered by this description.
Fibrotic events	Routine pharmacovigilance	None
Substance abuse/Drug dependence	Routine pharmacovigilance	None
Response-based behaviour	Routine pharmacovigilance	None
Hyperreflexia	Routine pharmacovigilance	None
Dystonia	Routine pharmacovigilance	None
Overdose	Routine pharmacovigilance PERIODIC REVIEW IN THE BI GLOBAL DRUG SAFETY DATABASE	Routine risk minimisation activities. The following information is included in section 4.9 of the SmPC (Overdose): *There is no clinical experience with massive overdose. The expected adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdose of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.*
Medication error	Routine pharmacovigilance; Intensified monitoring of post-marketing reports; PERIODIC REVIEW IN THE BI GLOBAL DRUG SAFETY DATABASE	Internal Communication and Training on specific adverse event processing with regard to formulation. Additional instructions on the outer carton of the prolonged-release tablet: *Once daily. Swallow whole, do not chew, divide or crush.* The following information is included

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		in Section 4.2 of the SmPC for prolonged-release tablets. *{TRADE NAME} prolonged-release tablets are a once-a-day oral formulation of pramipexole. The tablets should be swallowed whole with water, and must not be chewed, divided or crushed.* The following information is included in Section 3 of the PL for prolonged-release tablets (together with a pictogram): *Take {TRADE NAME} prolonged-release tablets only once a day […].* *Swallow the tablets whole with water.* *Do not chew, divide or crush the prolonged-release tablets. If you do, there is a danger you could overdose, because the medicine may be released into your body too quickly.*

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The new strengths of 1.57 mg and 2.62 mg of prolonged-release tablets have been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The results of the tests indicate that the drug product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

Non-clinical pharmacology and toxicology

No new non-clinical studies have been conducted in the context of this submission for registration of the two additional dose strengths 1.57 mg and 2.62 mg pramipexole prolonged release.

Efficacy

No new Phase I or Phase III trials have been conducted in the context of this submission for registration of the two additional dose strengths 1.57 mg and 2.62 mg pramipexole prolonged release.

Safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Having considered the safety concerns in the

risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Sifrol in the 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) was favourable and therefore recommended the granting of the marketing authorisation.