European Medicines Agency

London, 18 February 2010
Doc.Ref.: EMA/816879/2009

WITHDRAWAL ASSESSMENT REPORT FOR NENAD

International Nonproprietary Name:
lisuride

Procedure No. EMEA/H/C/001020

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

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8613
E-mail: mail@ema.europa.eu http://www.ema.europa.eu
©EMEA 2010 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Axxonis Pharma AG submitted on 12 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Nenad, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 21 June 2007. The eligibility to the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for the following indications:
For Nenad transdermal patch 2.5 micrograms/h and 5 micrograms/h:
1) the treatment of the signs and symptoms of restless legs syndrome; and
2) the treatment of idiopathic Parkinson's disease in combination with levodopa

For Nenad, 2.0 mg powder for solution for infusion:
Nenad infusion is indicated for the controlled parenteral therapy of advanced idiopathic Parkinson's disease.

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the following countries: Switzerland.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Hans Winkler
Co-Rapporteur: Barbara van Zwieten-Boot

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 12 May 2008.
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2008.
- During the meeting on 22-25 September 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2008.
- The summary report of the GCP inspection of study TULIP IIb (indication treatment of idiopathic Parkinson's disease in combination with levodopa) carried out at the two investigator sites in Romania (dates of inspection: 29/09/08 - 01/10/08 and 21-24/10/08) and at the sponsor site (dates of inspection: 13-17/10/08) was issued on 7th of January 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 May 2009.
- The applicant withdrew the MAA for Nenad subcutaneous infusion on 18 May 2009.

- During the CHMP meeting on 26-29 May 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant. The final list of outstanding issues was sent to the applicant on 29 May 2009.
- The applicant submitted the responses to the CHMP list of outstanding issues on 21 August 2009.
- The applicant withdrew the MAA for Nenad in the treatment of Parkinson's disease on 31 August 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 September 2009.
- During the CHMP meeting on 19-22 October 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Nenad on 19 November 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Restless Legs Syndrome (RLS) is a sensori-motor neurological disorder that is estimated to affect age-dependently between approximately 3 and 10% of the total population. Age of onset is known to vary widely, and variations in the clinical course with periods of remission are especially common in young adults. RLS is characterized by an urge to move the limbs, mainly the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. The symptoms begin or worsen during periods of rest or inactivity and are partially or totally relieved by movement. Typically, symptoms occur or worsen in the evening or night. Whilst neurological examination usually is normal, sleep disturbances and periodic limb movements during sleep (PLMS, as revealed by polysomnography and actimetry) are frequent. The pathophysiology of RLS is not yet well-understood. There appears to be an "idiopathic" form (60 to 80%) of genetic or unknown origin (familial in 40 to 60%) and secondary forms associated with various causes. Secondary forms (20 to 40%) include patients with renal failure and uremia or undergoing dialysis, iron deficiency, hypothyroidism, rheumatoid arthritis, pregnancy, spinal disorders, polyneuropathy or diabetes mellitus.
Approximately a third of the patients reporting RLS symptoms may need medical treatment (Henning, 2004). Patients who need continuous treatment are mostly older than 50 years. Severe RLS is mostly a chronic progressive disorder that, once started, may need life-long treatment (Trenkwalder et al. 2005). Currently dopaminergic therapy is considered to be the most effective treatment, although the mode of action is not known (EURLSSG/Trenkwalder et al. 2007). Currently licensed dopaminergic therapies for moderate to severe idiopathic RLS include perorally administered ropinirole and pramipexole. Recently, transdermal rotigotine (patch) obtained a positive EMEA-opinion.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended – complete and independent application.

The indications for which the applicant initially applied was for Nenad Transdermal Patch 2.5 and 5 micrograms per hour 1) the treatment of the signs and symptoms of Restless legs syndrome; and 2) the treatment of idiopathic Parkinson's disease in combination with levodopa. For Nenad 2.0 mg powder for solution for infusion, the initially applied indication was for the controlled parenteral therapy of advanced idiopathic Parkinson's disease. During the procedure, the applicant has modified the claims and the applied indication was restricted to the treatment of the signs and symptoms of moderate to severe idiopathic restless legs syndrome in adults. The indication for Parkinson's disease was withdrawn during the assessment procedure due to major objections on clinical efficacy and safety from the CHMP. The clinical trials for the Parkinson's indication are therefore only briefly summarised in this report.

2.2 Quality aspects

Introduction

Nenad is a transdermal patch used for the treatment of Restless Legs Syndrome. The active substance in the Nenad patch is lisuride, i.e., a dopamine agonist which stimulates dopamine receptors in the brain. Nenad contain 2.5 mg respectively 5 mg lisuride (nominal release rate of 0.06 mg of lisuride per 24-hour interval). Each Nenad patch is individually packed into a heat-sealed white paper/aluminium foil/polyethylene laminate sachet. Each pack contains 5 or 15 aluminium foil sachets.

Nenad is presented as 10 cm^2 and 20 cm^2 transdermal patches containing 2.5 mg and 5 mg of lisuride, and designed to release 2.5 µg/h and 5 µg/h, respectively.

Each patch is composed of five layers:

- a backing layer consisting of a transparent siliconised polyester film,
- an UV-protective overtape containing a polyisobutylene adhesive and UV absorber, covered with a transparent polyethylene backing film
- an intermediate layer, consisting of a thin polyester film,
- a self adhesive matrix layer containing lisuride, butylated methacrylate copolymer, succinic acid, dibutyl sebacate
- a removable protective layer, which is a transparent siliconised polyester film (to be removed prior to application of the patch).

Drug Substance

The active substance is lisuride (3-(9,10-Didehydro-6-methyl-8α-ergolinyl)-1,1-diethylurea). Lisuride is a semi-synthetic ergot alkaloid derivative synthesised from erginine in two steps followed by various purification steps. The Active Substance Master File (ASMF) procedure was followed for the active substance.

Lisuride is an almost white to light yellow or brownish crystalline powder. Lisuride is slightly soluble in methanol, ethanol, dimethylformamide, dimethylsulfoxide, chloroform and dichloromethane, sparingly soluble in ether and practically insoluble in water and hexane. Lisuride structural formula is as follows:

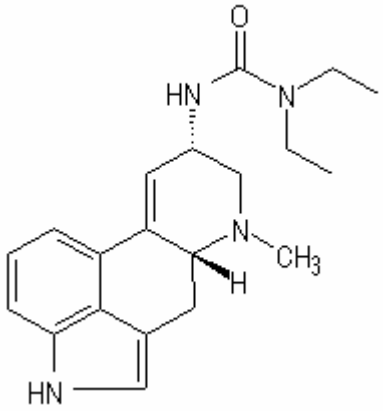


Figure 1: Chemical structure of lisuride

The active substance used for manufacture of the finished product is the anhydrous form of lisuride free base. The active substance is completely dissolved during the manufacturing process and remains dissolved in the finished product. Thus, the original crystal form of the active substance does not have any influence on the properties of the drug product.

The logP (octanol/water) of lisuride at pH 7 was estimated to be 1.3 and the melting point was 189.5 °C. Lisuride has a pKa value of 7.2 and is therefore a weak base. Due to its physico-chemical characteristics lisuride appears to be a suitable candidate for transdermal drug delivery.

- Manufacture

Lisuride possesses two chiral centres at C-5 and C-8. Among the four possible isomers only the 5R, 8S has been described as the active substance lisuride. The 5S, 8R enantiomer is L-lisuride. Racemisation is measured by capillary electrophoresis and the levels of the L-isomer were found to be below the limit of detection. The NMR data confirmed the 5R, 8S configuration.

Confirmation of the chemical structure of lisuride was provided by mass spectrometry, proton and carbon NMR, infrared spectroscopy and UV spectroscopy.

Crystallisation of lisuride from various solvents showed that there are three polymorphic forms of lisuride. X-ray single crystal structure determinations indicated that form I is unsolvated anhydrous form, form II is a lisuride ethanol solvate and form III is a lisuride methanol solvate. All the batches produced comply with the pattern corresponding to the crystal structure of lisuride form I.

These results confirmed that the active substance has the proposed structure when synthesized by the proposed manufacturing process.

- Specification

The active substance specification includes tests for appearance (visual examination), identification (HPLC and optical rotation), assay (HPLC), related compounds (HPLC), water content (PhEur), residual solvents (GC), heavy metals (PhEur) and sulphated Ash (PhEur).

Batch analysis data was provided on two batches confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Stability studies were performed on two batches of lisuride stored at 5^{o}C (long term conditions) for 36 months and at 25^{o}C / 60% RH (accelerated conditions) for 60 months. The stability data showed that lisuride stored in double polyethylene bag in aluminium can at a temperature of 5 ± 3^{o}C comply with the specifications.

The stability studies showed that the active substance is stable and confirm the proposed re-test period.

Drug Product

- Pharmaceutical Development

Nenad has been developed as matrix type transdermal patch. The active substance is homogeneously dispersed in a self-adhesive matrix. The two different dosage strengths of the finished product have the same composition and differ solely in the size of the active laminate, i.e., the 2.5 µg/h patch is 10 cm^2 in size and the 5 µg/h patch is 20 cm^2 in size. The patches are individually packed into a heat-sealed white paper/aluminium foil/polyethylene laminate sachet.

The compatibility with the active substance was demonstrated with the results of the stability studies performed on the finished product.

Additional efforts were made to ensure that crystallisation of the active substance in the patch did not occur throughout the shelf life of the product. This is an important issue for transdermal patches since

crystallisation might result in a decrease in thermodynamic activity of the active substance in the patch, and thus decrease in drug permeation.

Excipients were pharmacopoeial grade or were tested according to in-house monographs. The analytical procedures have been satisfactory validated.

Since lisuride is sensitive to light, to protect it during the application to patients, an overtape overlapping the active matrix containing an UV adsorbing substance was developed. Polyisobutylene based pressure sensitive adhesive was chosen. The UV absorber had not been used before in topical formulations and was therefore considered to be a novel excipient. However, full characterisation has not been provided.

- Manufacture of the Product

The manufacturing process involves the following operations: preparation of the coating mass and the drug containing adhesive matrix under light protection and nitrogen atmosphere. All excipients are dissolved in the processing solvents and added under slow stirring. The drug containing adhesive matrix is coated onto the PETP foil using a continuously working coating line with a four-section dryer. Increasing temperatures are set to remove the process solvents. The dried matrix is laminated with the PETP foil and wound up. The UV-protective overtape is manufactured by preparing a coating mass (adhesive, UV absorber and solvents) which is coated onto the release liner. The solvents are removed in a four-zone dryer by applying increasing temperatures. The adhesive matrix is covered with a PE backing foil. The rolls are trimmed and rolled up. Finally, the rolls of the finished laminate are further processed, i.e., by die cutting, assembling and pouch packaging. Satisfactory in-process controls have been defined at each stage of manufacture.

The manufacturing process was considered non-standard since the finished product is a modified release dosage form. The results of the first validation batch show results which are not always within specification. Nevertheless, the additional results of in-process controls during the coating process of three clinical batches (with final production scale) underline the reproducibility and robustness of the entire manufacturing process.

- Product Specification

The product specifications include methods for appearance (visual examination), identification (HPLC and UV), lisuride assay (HPLC), content uniformity (HPLC), degradation products (HPLC), residual solvents (capillary GC) microbial purity (Eur.Ph.), adhesive properties (adhesive strength and separation power) and dissolution. The acceptance criterion for the dissolution test is acceptable and has suitable discriminatory properties. Therefore, satisfactory control of batch-to-batch consistency can be achieved for the finished product. Degradation products are controlled and the limits are justified by reference to stability studies.

Certificates of analysis for the reference standards and reference materials used for the validation of the analytical methods for the determination of lisuride and the related substances were provided.

The finished product specifications have been justified and all methods of analysis have been described and adequately validated.

Batch analysis data on three batches of each strength was provided. The results comply with the specifications at the time of manufacture.

- Stability of the Product

Stability data on the product has been provided of two pilot scaled batched and one production scaled batch of 10 cm^2, and one pilot scale batch and two production scaled batches of 20 cm^2 batches stored at 25 °C/60% RH (long term conditions) for 36 months, 30 °C/65% RH (intermediate conditions) for up to 12 months and 40 °C/75% RH (accelerated conditions) for 6 months. Three batches were also

stored at 5 °C to assess crystal formation. Analytical methods employed were the same as those used for release testing.

The shelf-life has not been fully establish since stability results of three production scaled batches of each patch size with the required updated specification regarding the parameters dissolution testing and adhesive properties have not been provided.

Discussion on chemical, pharmaceutical and biological aspects

The active substance has been adequately described. Most excipients used in this transdermal patch are well known excipients with the exception of the UV absorber, which has never been used via the cutaneous route. Full characterisation was deemed necessary but not provided. The manufacturing process was considered non-standard since the finished product is a modified release dosage form. Results from one production scale batch complemented by three clinical batches confirmed the robustness of the process. The shelf-life has not been fully establish since appropriate stability data with the required updated specification regarding the parameters dissolution testing and adhesive properties have not been provided.

2.3 Non-clinical aspects

Introduction

GLP certification is available for most of the pivotal studies relevant to the current application. Other studies were conducted according to the best standard at the time (i.e. 1980s). These non-GLP studies were not considered to compromise the scientific integrity or affect the experimental results.

Pharmacology

- Primary pharmacodynamics

Lisuride has affinities for all known dopamine receptors, for 5-HT and for noradrenergic receptor subtypes. It has strong agonist effects at D2 and D3 receptors but also binds strongly to D4, D5 and D1 receptors; regarding the last one it can be considered to be a partial agonist. As a strong 5-HT_{1A} agonist, it reduces central 5-HT neurotransmission by autoreceptor activation, and it is a most potent antagonist at all 5-HT_{2B} receptors. Also regarding other 5-HT_2 and noradrenergic receptors it can be considered to be a partial or full antagonist. Lisuride is active in all central dopaminergic systems in intact animals and even more so in dopamine depleted animals used as models of Parkinson's disease.

The nigrostriatal system and the nucleus accumbens of intact rodents are affected by lisuride in a dual way. At low dosages ($\leq$ 0.025 mg/kg subcutaneously or orally) lisuride reduced spontaneous motor behaviour whilst higher doses induced stereotyped behaviours such as constant sniffing, licking or gnawing and increased motor activity. This apparently reflects dopamine (DA) autoreceptor stimulation by lisuride at low dosage and activation of postsynaptic DA receptors at higher dosages.

Behavioural and electroencephalographic (EEG) arousal, excitation, aggressiveness, and hypersexuality observed with high dosages of lisuride in rats may by related at least in part to activation of the mesolimbic-mesocortical dopamine system. The hypersexuality is clearly also caused by a functional serotonin antagonism.

- Secondary pharmacodynamics

Stimulation of dopamine receptors in the chemoreceptor trigger zone of the medulla causes the emetic effect of lisuride seen in dogs. The prolactin-lowering action of lisuride is caused by activation of dopaminergic receptors on the prolactin cells of the anterior pituitary which inhibits prolactin release from the anterior pituitary into the systemic circulation.The lowering of serum prolactin level leads to reduced or stopped lactation. Mounting behaviour occurring in grouped animals was attributed to effects on the serotoninergic system. This observation correlates with reports from Parkinson's disease patients who display symptoms such as increased libido or hypersexuality.

It could be demonstrated by the use of pooled brain samples from male Wistar rats that lisuride significantly influences the balance of several transmitters. The levels of 5-HT, DA, and NA were increased after treatment with lisuride, whereas the levels of 5-hydroxyindolacetic acid (5-HIAA, the main metabolite of serotonin), DOPA, and 5-HPT (5-hydroxytryptophan) were decreased.

Lisuride showed in rats a dose-and time-dependent hypothermic action which could be reduced by pre-treatment with the classical DA antagonist haloperidol. Activation of dopaminergic systems in the hypothalamus is probably the basis for the hypothermia and anorexia observed in lisuride-treated rats.

- Safety pharmacology programme

Cardiovascular effects
Cardiovascular parameters were studied in several species (rat, rabbit, cat and monkey) after acute administration of lisuride. No direct chronotropic or ionotropic effects were observed in isolated spontaneously beating atria. However, lisuride decreased blood pressure and heart rate in non-vagotomized normotensive rats. The bradycardia was blocked by vagotomy.

Lisuride has never been associated with a proarrhythmic risk in patients, but a full non-clinical safety programme was designed and conducted in order to fully study the potential effect of lisuride on ventricular repolarisation. The whole-cell patch-clamp technique was used to investigate the effects of lisuride hydrogenmaleate on HERG potassium channels stably expressed in HEK 293 cells. Lisuride was tested in concentrations of 0.3μM, 1 μM, 3 μM and 10 μM (n = 4 cells). The results showed that a lisuride hydrogenmaleate concentration approximately 50 times higher than the highest expected therapeutic plasma level of 0.006 μM (2ng/ml) in patients does not significantly inhibit the HERG outward tail current.
A study was designed to evaluate the effects of intravenously administered lisuride hydrogenmaleate on the heart rate, blood pressure and electrocardiographic (ECG) parameters in male cynomolgus monkeys (4 animals/dose) using a telemetry system. Slight blood pressure and heart rate lowering were observed in this study but these findings are classical and related to the dopamine agonist properties of lisuride. No treatment-related changes were noted in the PR interval and QRS duration. The few prolonged QT` intervals after initiation of infusion were considered as unlikely to reflect delayed ventricular repolarisation.

Respiratory effects
The potential effects of lisuride (single intravenous administration of 0.0625, 0.125 or 0.25 mg/kg) on respiratory function were evaluated in rats by means of whole body plethysmography. Respiratory rate and peak inspiratory and expiratory flows (PIF and PEF) were significantly increased at all dose levels except at the lowest dose of 0.0625 mg/kg. The effects on PIF and PEF indicate a physiological adaptation to pharmacologically induced hyperactivity.

Metabolic and diuretic effects
Studies in rats indicated that, similarly to methysergide, lisuride has a blood glucose-increasing action. In addition, there was a rise of serum free fatty acids and insulin levels after acute oral administration of 200 μg/kg of lisuride. After 10 days treatment with this dosage, the free fatty acids and insulin values were in the control range although blood glucose levels were slightly elevated.
In rats given lisuride (30 or 300 μg/kg) by continuous intravenous infusion to produce continuous urinary flow, a transient antidiuretic effect was followed by excessive hyperexcretion of electrolytes and water. A transient decrease of blood pressure, associated with a reduction of renal blood flow and adrenergic counter regulation with increased lipolysis and glycogenolysis as well as relatively diminished insulin secretion in rats can be presumed to be the cause of these findings.

Drug Dependence
Drug dependence potential of lisuride was assessed in cross-physical dependence tests. Lisuride at 15 and 60 μg/kg subcutaneously suppressed neither morphine nor barbital withdrawal signs in monkeys that were physically dependent on the respective drugs and withdrawn. These results indicate that lisuride does not possess any cross-physical dependence on morphine or barbital. Self-administration experiments showed as well that CNS and behavioural effects of lisuride appeared to be quite different

from those of LSD and amphetamines; the dependence potential of lisuride (at 1 to 4 µg/kg intravenously) was very low, if any, and its abuse liability was assumed to be low, because of the lack of LSD- or amphetamine-like behavioural effects and its very low dependence potential.

- Pharmacodynamic drug interactions

The effects of lisuride (0.1 – 12.5 mg/kg subcutaneously) on the anticonvulsant efficacies of various antiepileptic agents (phenytoin, ethosuximide, and phenobarbital sodium) were tested in the maximal electroshock test in the mouse. Simultaneous administration of lisuride slightly reduced the anticonvulsive effects of these agents. The possibility of a synergistic effect of lisuride on barbiturate hypnosis was investigated in mice and rats. Administration of doses ranging from 0.78 to 12.5 mg/kg showed that lisuride at higher doses antagonizes the hypnotic action of barbiturates at the level of the CNS in mice and rats, rather than showing a synergistic effect.

Pharmacokinetics

The pharmacokinetics of lisuride has been studied in several animal models. However, some of the experiments have been performed several decades ago and the applicant submitted specifications regarding the analytical methods in a very sparse way. At the request of the CHMP, the applicant submitted a more detailed elaboration of the analytical methods during the assessment procedure.

Absorption

Pharmacokinetic studies were performed in rats, rabbits, rhesus and cynomolgus monkeys. Routes of administration were oral, intravenous, subcutaneous and intraduodenal (in one specific experiment).
Single dose applications comprised oral, intravenous or subcutaneous injections. Regarding the transdermal use, no additional *in vivo* PK studies were carried out.

In all animal species, lisuride was well absorbed after oral administration of doses ranging from 0.1 to 5 mg/kg. Although 80 % absorption was estimated on basis of excretion data, it can be assumed that absorption was complete and excretion data merely reflected small differences in the quantity of differently cleared metabolites in dependency of the route of administration.
Although almost completely absorbed, the oral bioavailability of lisuride was low and dose dependent. This is due to rapid metabolism reflected by metabolic clearance rates (MCR) which were either equal or even higher than the theoretical plasma flow of the liver in animal species and in man. As an effect of high MCRs, lisuride undergoes a hepatic first-pass effect reducing oral bioavailability to 6-12 % of dose in rabbit and monkey and to 30-40 % in the rat.

Bioavailability after subcutaneous infusion was fast and approximately complete. After intravenous or subcutaneous administration, the initial decline in plasma levels was fast with a half-life of 1 to 2 h, followed by another phase with a slower decline. Inter-individual variation in plasma levels of lisuride and total radioactivity was considerable.

After continuous subcutaneous infusion for several weeks in rats and cynomolgus monkey, plasma concentrations were approximately dose-proportional. In cynomolgus monkey, the plasma level at the highest dose of 2 mg/kg/day may be less than dose proportional.

The penetration enhancers azone, lauryl alcohol and lauric acid in propylene glycol considerably increased the lisuride flux through the skin of hairless mice in the Franz-Chamber-Model.

Distribution

Following intravenous injection, wide distribution of the compound occurred only for a short period of time. The rapid decline is in agreement with the high clearance of lisuride. The tissue/plasma ratio of some tissues such as liver, kidney, and lung increased after multiple dosing of lisuride. It is considered likely that the accumulation of radioactivity in rat tissues after repeated dosing is due to the accumulation of some metabolites. As rats follow a different biotransformation pathway than primates, the data are too few to conclude whether and to what extent accumulation of metabolites occurs in other species such as monkeys.

Lisuride crosses the blood/brain and the blood/placental barrier, whereas the distribution within the brain is not even. According to the known low bioavailability following oral treatment, lisuride was found mainly in the gastro-intestinal tract and liver.
The blood-plasma ratio of rats increased considerably with repeated dosing, from a ratio of about 1.4 at 24 h after dosing to a ratio of 2.5 (females) and 3.7 (males) at 24 h after 14 daily doses. The blood-plasma ratio in other species were around 1 and do not seem to increase over time. This suggests that lisuride metabolites in rats may have higher affinity to erythrocytes than in other species, possibly due to the formation of other metabolites than in other species.

Metabolism
Metabolites of lisuride do not seem to contribute to the pharmacology of lisuride.
Major inhibition by lisuride was observed with all five concentrations (0.1; 0.3; 1; 3; 10µM) of lisuride for CYP2D6 (60.1–81.2%) and at the highest concentration of 10 µM for CYP3A4. The Applicant stated that inhibition of the CYP enzymes at the therapeutic plasma concentration is supposed to be very unlikely. However, since lisuride is foreseen to be used in combination with other agents the importance of this finding cannot be ruled out.

Excretion
The excretion of lisuride was studied in several different species including rat, non-human primates, rabbits, and healthy volunteers following different routes of administration. Lisuride is almost not excreted unchanged but in the form of metabolites. In rat, about 10-20% of the radioactive dose is excreted via urine, and 70-80% via faeces. In rabbit, rhesus monkey and cynomolgus monkey the fraction excreted via urine is higher, up to 45% of dose. Excretion data in man showed complete elimination of all metabolites, whereas the elimination ratio of urine/faeces was 1:1. Lisuride is also excreted via milk. It has been demonstrated that milk levels correspond to roughly 20- 30 % of drug plasma levels. Because lisuride decreases prolactin secretion in humans, lactation will be inhibited.

Pharmacokinetic interaction studies
No studies were conducted.

Toxicology

- Single dose toxicity

The acute toxicity of lisuride was investigated in the mouse (subcutaneous, intravenous and intragastric routes), the rat (intragastric route), the rabbit (intragastric and intramuscular routes) and the Rhesus monkey (intravenous and intragastric routes). The acute toxicity of lisuride is low. For rats kept in groups, oral LD_{50} values were much lower than for those kept in isolation, which may be due to a group effect similar to amphetamine, a phenomenon only seen in this species.
The highest tested dose without mortality after subcutaneous and intravenous application in the mouse was 125 mg/kg and 12 mg/kg, respectively. The most common noteworthy findings in all tested animal species were tremor, hyperactivity, moderate apathy, and convulsions. The rabbits exhibited cramp-like muscle contractions, tremor, ventral or lateral decubitus, and some animals suffered dyspnoea and emitted squeals. The principle symptoms in the monkeys were apathy and dose-dependent ataxia. Respiratory distress occurred in the monkeys after 0.2 mg/kg intravenously, whereas at 0.05 and 0.1 mg/kg intravenously only transient apathy and ataxia as well as anxiety and agitation were seen.

- Repeat dose toxicity

Repeat dose toxicity studies were carried out by continuous subcutaneous infusion, by intravenous injection or by intra-gastric administration in Wistar-Han rats and in Cynomolgus and Rhesus monkeys, and by intra-gastric administration in dogs.
No toxic organ lesions were found in rats after 4 weeks continuous s.c. administration of lisuride hydrogen maleate (LHM). Findings of the pivotal 28 weeks study included clinical observations (stereotyped behaviour), changes in clinical biochemistry parameters (decrease in serum cholesterol, urine volume), endocrine alterations (decrease in circulating prolactin levels, increased corpora lutea, signs of an increased activity of the adrenal cortex) as well as decrease in thymus weight. The No Observed Adverse Effect Level (NOAEL) was < 0.1 mg/kg bw.

The dogs showed vomiting after repeated intragastric administration of lisuride at 0.0005 or 0.015 mg/kg/day for 3 days. As such the dog appeared not to be a suitable species for long-term studies.

A dose-range study was carried out in cynomolgus monkeys after continuous subcutaneous infusion of LHM 0.1, 0.3, or 1.0 mg/kg/day over a period of 4 weeks. The animals developed severe skin lesions (marked to severe phlegmones) which partly caused an unscheduled discontinuation of treatment. The investigator concluded that these symptoms might have been caused by drug-related effects on the immune system. In addition, subcutaneous application of lisuride at the lowest dose (of 0.1 mg/kg bw) still led to mortality in about one third of the animals. Based on these data, no conclusions with regards to the NOAEL can be drawn. Obviously, the dosing of the monkey study was based upon excellent tolerability data observed in another monkey species with oral lisuride, but very unexpectedly a comparable drug load infused continuously in cynomolgus monkeys resulted in an exacerbation of pharmacological effects. Studies in all kinds of advanced Parkinson's disease patients with poor responses had shown no comparable symptomatology.

In one additional study, LHM was administered during a time course of 26 weeks in cynomolgus monkeys using dosages of 0.1, 0.3 and 1.0 mg/kg/day. The continuous s.c. infusion led to an unexpected increase in mortality of 3/10, 5/10 or 7/10 monkeys at the low (0.1), mid (0.3) and high dose (1.0) level associated with atrophic changes of the lymphoid organs as well as some alterations of clinical biochemistry (elevation of serum enzymes). The observed increased mortality was associated with atrophic changes of the lymphoid organs, which in turn was considered to be the consequence of a final refusal of food uptake (caused by continuous stress).

- Genotoxicity

Several genotoxicity studies have been performed. Despite of the weak positive results in the Ames test in the two salmonella strains (TA1538, TA98), lisuride did not raise any further concerns as risk factor for mutagenic or carcinogenic effects *in vivo*.

- Carcinogenicity

There were no indications for a carcinogenic potential of lisuride. With the exception of a slightly increased incidence of Leydig cell tumours at the high dose level, some evidence even suggested that lisuride had an inhibitory effect on tumour formation. E.g. the incidence of certain tumours in mice (murine leucosis and carcinoma of the lungs in males and pituitary hyperplastic nodules/microadenomas and ovarian cystadenomas in females) was reduced. Increased incidence of Leydig cell tumours was explained by the possibility that these tumours could not be clearly distinguished from nodular hyperplasia which in turn is a consequence of increased secretion of the luteinising hormone.

- Reproduction Toxicity

The potential effects of lisuride on reproduction have been evaluated in rats (fertility and early embryonic development, pre and postnatal development) and in rats, Cynomolgus monkeys, and rabbits (teratology).
Administration of lisuride 0.1 mg/kg led to adverse effects on fertility and pregnancy rate in rats. Following applications of lisuride at higher dosages of 0.3 and 1.0 mg/kg none of the inseminated rats became pregnant. The described malformations (in rabbits and Cynomolgus monkey) did not seem to be compound-related. However, the number of foetuses available for drawing any conclusions was quite low.
Lactation of rats was dose-dependently disturbed from 0.1 mg/kg onwards. At 0.1, 0.3 and 1 mg/kg the mean pup weights were decreased in comparison with the controls. At 1.0 mg/kg all pups had died by day 7 post partum, and at 0.3 mg/kg pup losses occurred throughout the lactation period and continued to occur after weaning.

- Local tolerance

Local tolerance has primarily been evaluated in rabbits but, to limited extent, also in mice. Parenteral administration of lisuride elicited only negligible local reactions after intra-arterial injection. Also

paravenous or intramuscular administration of lisuride caused no substance related local irritant effects.
In two local tolerance studies in rabbits using the transdermal system (TDS) for comparison of placebo TDS with lisuride TDS, the test item was held in contact with the skin for 24 hours by means of an occlusive hypoallergenic dressing. The transdermal patch was slightly irritant on scarified and non-scarified skin in rabbits. The reaction was similar for placebo patch and the lisuride patch. Full recovery of the skin lasted up to 8 days.
Considering that transdermal patches are thought to be used as long-term therapy in humans the applicant was asked during the assessment procedure to justify the lack of prolonged and repeated dose dermal tolerance tests by using the TDS system similar to the clinical use. The applicant has adequately addressed this issue by submitting two studies in rabbits and guinea pigs. The animals were treated with the normal lisuride 10 cm² or placebo patches being applied on abraded as well as on non-abraded skin every 48 hours for 4 weeks with further protection (against scratching or contamination) provided by a hypoallergenic semi-occlusive aerated dressing (overtape). This study in rabbits demonstrated that, by comparing the test item to the placebo, the incidence and severity of the reactions were slightly less in the placebo group. In guinea pigs the dermal application of the lisuride patch appeared to be well tolerated under the experimental conditions of this study.

- Impurities/metabolites

No studies on metabolites have been performed. This is considered acceptable. The metabolic profile of lisuride in liver microsomes of various species did not indicate that in humans specific metabolites were formed that were not formed in any of the animal species. In addition, although quantitatively different, the same metabolites were encountered in urine of man and Rhesus monkey.

In the drug substance, the impurities erginine and ergine are qualified by the limit <0.05%, 8α-ethylcarbamate by the limit <0.15% and β-lisuride, diethylamine and other potential impurities by the limit <0.10% (ICH Topic Q3A (R2), CPMP, ICH/2737/99). The impurities lisuride ethylcarbamate, lisuride N-oxide, 8α-aminoergolene have been toxicologically qualified since in the Lisuride Transdermal Patch the proposed limits for these impurities at the end of shelf life (≤1.0% for lisuride N-oxide and 8α-aminoergolene and ≤0.5% for lisuride ethylcarbamate) does not exceed the qualification threshold of 1.0% of identified impurities in the drug substance (ICH Topic Q3B (R2), CPMP, ICH/2738/99).

The lisuride patch includes an overtape containing a UV protective agent, which is in direct and indirect contact with the skin. In view of the applicants provided data, no toxic effects are expected for the UV absorber, if used as an excipient in the transdermal patch. However, the applicant has not provided the original studies on the irritation/sensitization and the genotoxicity of the UV absorber. This issue was not resolved during the procedure.

- Other toxicity studies

Photostability testing of the lisuride patch (with an overtape containing the UV protective agent) with or without a pouch has been performed after an exposure of 8, 16 and 38 hours, respectively. According to the study protocol, photostability testing about 16 and 38 h of Lisuride TDS Verum without pouches showed degradation of the active ingredient and therefore an increase of known and unknown impurities.

Even very limited light source causes coloration (light yellow, light brown) of lisuride solution after few minutes. It can be concluded that lisuride undergoes some reactions in solutions which decompose this product. When exposure time is sufficiently long (few hours – depends on light intensity) no original lisuride has been found in solution and formation of more then 20 compounds was observed (as determined by HPLC).

Lisuride in solution when exposed to the light undergoes various reactions, namely oxygen radicals' uptake (as revealed by ESI-MS). The major products were compounds containing 2 oxygen atoms but traces of compounds containing 3, 4, and even 5 oxygen atoms could be detected in the mixture. Further, the oxygen uptake is supposed to be one of the two main degradation pathways, besides

formation of dimers and higher oligomers (reactions common for all ergopetines, as determined for ergotamine).

During the assessment procedure, the applicant provided additional data on the phototoxic potential of lisuride. A study was conducted with the original lisuride and placebo patch formulations in guinea pigs. In addition, the applicant performed a controlled clinical study in healthy volunteers to determine the minimal erythema dose as recommended in the EMEA Note for Guidance on photosafety testing. The results of theses studies indicate that lisuride has the potential to cause local skin reactions characterized by erythema and in some cases oedema. These skin reactions can potentially be exacerbated by exposure to UV irradiation. Skin coloration (brownish or greyish colour), due to oxidation products of lisuride remaining in the stratum corneum, occurred in all healthy volunteers at application sites exposed to lisuride.

The effect of lisuride on the immune system has not been evaluated. In the repeated-dose toxicity studies, a decrease in thymus weight has been observed after subcutaneous administration in rats (28 weeks) and monkeys (26 weeks) and after intravenous administration in rats (4 weeks), but not after intragastric administration in rats (28 weeks) and monkeys (at 52 weeks). This reduction in thymus weight was ascribed to stress. However, according to the guideline on immunotoxicity, the evidence for a stress-related immunotoxic effect should be compelling and a reduction in thymus weight is on its own considered to be insufficient (ICH S8, CPMP/167235/2004). In the 4-week dose-finding study in Cynomolgus monkeys, there was an increased incidence of infectious skin lesions from 0.1 mg/kg/d onward. This effect, due to a Staphylococcus aureus infection, was reported to be incidental, since it was not seen in the 26-weeks pivotal study in monkeys. The possibility that these infections could be related to an immune suppressive effect of lisuride has not been discussed by the applicant, however. As an antagonist of 5-HT2B receptors, lisuride is an inhibitor of cell proliferation in a number of cell types. Therefore, an immunotoxic effect of lisuride cannot be excluded based on its pharmacodynamic activity.

Ecotoxicity/environmental risk assessment
Lisuride is altering the concentration of the natural hormone prolactin and fulfils therefore the criteria of a potential endocrine disruptor. The potential of lisuride being an endocrine disruptor is additionally substantiated by the following facts: Studies from literature research show that the principal action of prolactin in fish is osmoregulation, although it is also implicated in reproduction, behaviour, growth, and immunoregulation. Ergot derivates with dopaminergic activity appeared to lead to reduced secretory activity and ultrastructural changes in prolactin cells in fish. In newts prolactin was found to have crucial functions in reproduction. Moreover lisuride has effects on insects and crustacea and has insecticidal activity. Endocrine alterations were anticipated after treatment with lisuride: decreasing levels of circulating prolactin in several studies covering rats, dogs and monkeys. Data demonstrate embryotoxic and endocrine effects in traditional laboratory animals in response to lisuride. Many authors have investigated hormonally events involved in reproduction and development and it was shown that there exist little differences between wildlife species and animal models.

Discussion on the non-clinical aspects
Lisuride is a dopamine agonist with affinities for all known dopamine receptors, for 5-HT and for noradrenergic receptor subtypes. Lisuride is active in all central dopaminergic systems in intact animals and in dopamine depleted animals used as models of Parkinson's disease. The acute toxicity of lisuride is low. In repeated dose toxicity studies, the major effects were interpreted as an expression of increased dopaminergic activity.

Several genotoxicity studies have been performed. Lisuride did not raise any further concerns as risk factor for mutagenic or carcinogenic effects *in vivo*. There were no indications for a carcinogenic potential of lisuride.

The potential effects of lisuride on reproduction have been evaluated in rats (fertility and early embryonic development, pre- and postnatal development) and in rats and rabbits (teratology). These studies do not indicate any teratogenic effects, but lisuride disturbed female fertility in that it dose-dependently decreased the pregnancy rates. Moreover, the embryo-mortality in rats was increased. The

applicant was asked to provide sufficient data proving that lisuride does not endanger embryonal or foetal development in humans. Furthermore, the applicant was asked to clarify the continuation of the pup losses after weaning as observed in one study in the rat. The applicant has adequately addressed these issues. The applicant refers to the clinical experience with cabergoline in the long-term high-dosed therapy of PD and also of prolactinomas. This use and all clinical experience obtained with dopamine agonists (and at lower dosages as used in RLS) have never led to specific endocrine or other adverse events. The continuation of the pup losses after weaning (as observed in one study in the rat) was explained by a reduced body weight, with this effect being carried on also during further growth of the F1 animals. In rats - but not in humans – lisuride also has an appetite-suppressant effect.

During the assessment procedure, the applicant submitted *in vivo* data on phototoxicity in guinea pigs which show that Lisuride or putative degradation products thereof cause skin irritation and that UVA irradiation (at $10J/cm^2$ for 45 minutes exposure) potentiates this effect (from grade 1 to grade 2). Therefore, lisuride has phototoxic properties. Issues that were not resolved during the procedure concerned that the applicant should better characterize the chemistry of the degradation products, and that a precise definition of sun light protections should be provided.

The lisuride patch includes an overtape containing a UV protective agent, which is in direct and indirect contact with the skin. In view of the applicants provided data, no toxic effects are expected for the UV absorber, if used as an excipient in the transdermal patch. During the procedure, the applicant was asked to provide the original studies on the irritation/sensitization and the genotoxicity of the UV absorber. This issue was not resolved.

Lisuride alters the concentration of the natural hormone prolactin and fulfils therefore the criteria of a potential endocrine disruptor. As a consequence, the applicant should conduct a phase II risk assessment according to EMEA Guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00). This issue was not resolved during the procedure.

2.4 Clinical aspects

Introduction

GCP
The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

- Absorption

From the patch, only 7% of the total dose was absorbed after 48 h application. Transdermal flux was calculated as 0.25 µg/h per cm² patch. C_{max} was achieved after 24 h. Lag-time at the first day was approximately 12 h. For safety reasons (i.e. local intolerance), the application term was limited to 48 hrs, but this is not necessary from a PK point of view, as plasma levels remained constant during continuous patch application for 3-4 days.
Bioavailability of sc infusion was nearly 100%. There was no lag-time, and t_{max} was estimated as 1 h after sc infusion.

- Distribution

Apparent volume of distribution was large (2.3-2.4 L/kg), and after bolus injection the distribution half-life was only 15 min, indicating rapid and intense distribution. Protein binding was moderate (approximately 77%), and interaction at protein binding level with other substances is not expected.

- Metabolism and elimination

Lisuride is excreted both by renal and biliary pathway, mainly in the form of (unidentified) metabolites. Half-life of lisuride is short (1.5-2 h), but mass-balance studies with C^{14} labelled lisuride showed that the metabolites circulate longer. The urinary excretion was biphasic. More than 90% of the renally excreted radioactivity was eliminated with half-lives of 7.7 ± 1.3 h after i.v. administration.

The remainder was excreted more slowly with a half-life of 23.4 ± 1.6 h. Fecal excretion was slower with most radioactivity being detected on days 2 and 3.

From in-vitro data, it became clear that the major metabolic pathway is mediated by multiple Cytochrome-P450 enzymes (CYP3A4 >1A1>2C9>2C19>2D6>2C8). CYP isoforms 1A2, 2A6, 2B6 and 2E1 were weak inhibitors *in vitro*. Of note, CYP2D6 may be more prominent pathway than could be concluded based on the in-vitro study, as lisuride exposure is significantly enhanced in poor metabolizers of CYP2D6, after oral application. There were no signs of auto-induction or auto-inhibition after long-term treatment.

The metabolic pathway is not completely clear. According to the Applicant, N-de-ethylation of the ethyl group at the ureum chain is the major metabolic pathway, followed by mono-oxygenation. However, the de-ethylated metabolite N-MDL was only recovered to low extent *in vivo*, and in human urine mainly double-oxygenated and double-de-ethylated metabolites were recovered.

- Dose proportionality and time dependencies

The available data with regard to dose proportionality and time dependency of TDS data were not sufficient to support these points. As requested in the "Note for Guidance on Modified Release Oral and Transdermal Dosage Forms" (CPMP/EWP/280/96), a demonstration that steady state has been reached should be mandatory. With regard to dose proportionality, linearity has not been demonstrated convincingly especially not for the repeated use, in which case according to the guideline at least PK data for the highest and lowest dose level should be performed.
The blood levels obtained with s.c. infusions of 1 to 4 mg are around or above 1 ng/ml. This is clearly above the levels achieved with lisuride TDS (20 cm² patch: 80 - 100 pg/ml) which corresponds to an oral dose of 6 x 0.2 mg. In this context one has to consider that a s.c. dose of 2.0 mg/day corresponds to an oral dose of 10 mg if one takes the low bioavailability of the latter formulation into account.

- Variability

Interindividual variability is high for lisuride. This is known from the oral form and also true for the new routes: in patch application 50-180 % in different studies, after sc infusion 25-50%. The doses need to be individually titrated. The limited patch strengths hamper fine tuned titration. Absorption was significantly lower (-45%) after application at the abdomen, compared to application of the upper arm.

- Special populations

Pharmacokinetics in special populations has not been sufficiently characterized. With regard to impaired renal function, 10 patients in a hemodialysis program and 10 patients with creatinine clearance below 15 ml/min were examined in one trial. However, no drug levels were measured. As lisuride is virtually completely metabolized before renal excretion, no significant accumulation of the parent drug is expected. Accumulation of metabolites may occur, but as these display no or low affinity for dopamine receptors, no clinically significant effect is expected.
No clinical data are available regarding lisuride exposure in patients with mild-moderate hepatic dysfunction. These patients should be dosed with care. Patients with severe hepatic dysfunction should not be treated with lisuride.
There is no trial with lisuride in children.
Lisuride exposure was markedly increased (AUC 19 fold higher) in poor CYP2D6 metabolizers compared to extensive CYP2D6 metabolizers after oral administration. CYP2D6 polymorphism had less impact on lisuride exposure when patches were applied (up to 3.4 fold increment of AUC levels in poor metabolizers compared to extensive metabolizers), probably because the first-pass effect is avoided after parenteral application. However, these data indicate that co-administration with CYP2D6 inhibitors may still lead to clinical relevant increments (3-fold) of lisuride plasma levels when the patch is applied.

- Pharmacokinetic interaction studies

In vitro
The *in vitro* cytochrome P450 inhibitory potential of lisuride was tested in human hepatocytes. Major inhibition (≥ 50%) was observed for CYP2D6 substrate at all tested concentrations (0.1 µM – 10 µM

of lisuride) in a dose-dependent manner. CYP3A4 was inhibited only at a concentration of 10 μM - a concentration far above maximum free drug levels in man (≤ 8.6 nM). Lisuride had no significant influence (< 25% inhibition) on CYP1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1 at clinically relevant concentrations (i.e. < 0.1 μM).

In vivo
No new *in vivo* interaction studies were performed with the formulations to be marketed. The applicant has submitted results from previously conducted *in vivo* interaction studies with oral and i.v. formulation.
The possible cytochrome P450 induction potential of lisuride was investigated in 6 female and 6 male healthy young subjects. Oral administration at doses up to 600 μg/d during 4-week treatment showed no induction of hepatic CYP3A4. Urinary excretion of 6ß-hydroxy-cortisol (biomarker for induction of CYP3A4) was unchanged. A median plasma lisuride level of 84 pg/ml was observed.
A drug interaction study with lisuride and erythromycin was conducted in an open, single-dose, 4-arm cross-over study with 12 healthy male subjects. Oral erythromycin was given in a dose of 1g bid for 4 days prior to the use of oral (200 μg) or iv (50 μg) LHM. The last tablet of erythromycin was given at the same time of lisuride tablet ingestion or at the start of infusion.
CYP3A4 inhibitor erythromycin blocked the first-pass effect and increased lisuride exposure of 80% after oral administration. However, lisuride exposure increased only to limited extent (30%) after the use of erythromycin when lisuride was administered as i.v. infusion.

Pharmacodynamics

- Mechanism of action

Lisuride is a strong D_2 receptor agonist and a partial antagonist/agonist at the D_1 receptor in the striatum, depending on state of the system tested. Lisuride has in addition agonist effects at D_3, D_4 and D_5 receptors. Lisuride has also a strong affinity to serotonin receptors. It is a strong 5-HT_{1A}-agonist and a pure serotonin 5-HT_{2B}-antagonist. The mechanism of action of lisuride in Restless Legs Syndrome has not been fully elucidated. Neuropharmacological evidence suggests primary dopaminergic system involvement.

- Primary and Secondary pharmacology

No specific in-vivo pharmacodynamic studies (blood pressure, ECG, EEG, etc.) were submitted. For most pharmacodynamic actions reference is made to the literature.
The effect on lisuride on sleep was compared to placebo in 4 subjects in a sleep laboratory setting (cross-over design). REM sleep latency increased from 8.7 (SD 6) to 14.6 (8.4) minutes after lisuride, whereas placebo had no effect. Subjects experienced more sleepiness and were less alert after lisuride. This is a known side-effect of dopamine agonists.
The applicant submitted several studies where prolactin was measured as marker for dopaminergic activity. However, prolactin is no suitable marker as there was no clear dose-response relationship and a ceiling effect is rapidly achieved with clinically relevant doses.
Very sparse data indicated a possible PK-PD relationship for treatment of PD with patches. From data of an oral lisuride study, it was concluded that some side effects like nausea were related to the absorption rate (t_{max} and C_{max}).

Clinical efficacy

1. Restless legs syndrome

For the treatment of Restless Legs Syndrome (RLS), 3 clinical studies were performed: One phase IIa proof of concept study (TULIR 01/01), a 12-week Phase II/III dose finding study (TULIR 02/01) and one 12-week phase III pivotal study (TULIR 03/01).

Study **TULIR 01/01** was a proof of concept, single centre study of Lisuride TDS (patches) in patients with idiopathic Restless Legs Syndrome. The study consisted of an open-label finding of the optimal

dose which was followed by a double-blind placebo-controlled study period. All of the ten selected patients completed the open-label study period. One patient was excluded from further treatment because she showed no improvement on the CGI scale. Therefore, only nine patients were randomized in the subsequent one week double-blind placebo-controlled study period.

During the open treatment period (Baseline to Week 2) the International RLS Study Group rating scale (IRLS) total score improved by -22.1 ± 11.6 (mean ± SD), the periodic limb movements (PLM)/hour time in bed as assessed by the actigraph was reduced by 54.4 ± 28.4/hour, indicating a relief from symptoms. During randomized continuation therapy with Lisuride TDS in the double-blind period (Week 3), the IRLS total score (-1.4 ± 5.9) and the PLM/hour actigraph measure (-6.0 ± 2.0) improved slightly; in contrast, the IRLS total score (+11.5 ± 10.9) and the PLM-Index (+20.3 ± 26.5) worsened in the placebo group.
In the double-blind period of this trial, those patients receiving active treatment applied more patches than the patients under placebo.

In summary, the study results provided a preliminary indication of potential therapeutic efficacy and early estimates of dose response in patients with idiopathic RLS.

- Dose response study

Study **TULIR 02/01** was a double-blind, randomized, multi-centre, four-arm, parallel-group, 12-week comparative phase II/III study. The aim of this study was to investigate the clinical usefulness of three fixed doses (2.5 mg/5.0 mg/10 mg) of transdermal lisuride (patches) in comparison to placebo and to determine which dose exhibited the most favourable efficacy and safety profile in patients with idiopathic or uremic RLS.

Study participants
210 patients (placebo 53; lisuride 2.5 mg = 53; lisuride 5 mg = 54; lisuride 10 mg = 50) were randomized and exposed to one of the treatments. Four patients with no post-baseline values for efficacy variables were not included in the Full Analysis Set (FAS). Thirteen patients with major protocol violations were excluded from the PPS (n=193). According to the applicant, 135 of the 210 randomized patients (64.3%) completed the double-blind part of the study. A summary of study TULIR 02/01 is shown in Table 1.

Table 1. Summary of dose-finding study in RLS, TULIR 02/01

Study number	**Study design**	**Study and control drugs**	**Duration**	**Clinical endpoints**
TULIR 02/01 Dose finding trial	Double-blind, randomized, placebo-controlled parallel groups, fixed dose n=210 (randomized) n=206(FAS) n=193 (PPS) n=135 (CS) (125 completed without major protocol violation) Lisuride : n = 157 Placebo : n = 53 Males and females	Lisuride TDS: 10 cm^2 (n = 53) 20 cm^2 (n = 54) 40 cm^2 (n = 50) placebo (n = 53) every 48h	● 3 to 14 days run-in period ● Day 1-8 titration period ●Day 9 - Week 12: maintenance period ● 1 week tapering-off period	Change of IRLS sum score from baseline to end of treatment Responder and remitter's analysis

1 patch = 10 cm^2 (2.5 mg); 2 patches=20 cm^2 (5.0 mg); 4 patches=40 cm^2 (10 mg); CS=completer set, PPS=per protocol set , FAS=full analysis set

Treatments
After the screening visit patients entered a run-in phase of at least 3 days. Double/blind treatment started at baseline with two patches (10 cm^2) every other morning in all four groups (Group A: 2 placebo patches; group B: 1 active and 1 placebo patch; Group C and D: 2 active patches). After one week all patients were switched to treatment with four patches every other morning as follows: Group A 4 placebo patches; B: 1 active and 3 placebo patches; C: 2 active and 2 placebo patches; D: 4 active patches. Patients continued double-blind treatment up to Week 12 after which there was a 1-week down-titration period. Treatment with lisuride patches could be continued for up to one year in an open-label extension study period in those patients who completed the double-blind period; thereafter patients could, at the discretion of the investigator, continue treatment for a maximum of five years.

Outcomes/endpoints
Efficacy was evaluated by measuring the difference by the International RLS Study Group Rating (IRLS total score) as the primary variable. The change from baseline to the end of double-blind treatment (Week 12) was tested using an ANCOVA and compared the three different Lisuride TDS doses to placebo in a hierarchical manner.
Secondary endpoints regarding the double-blind period included:
- IRLS: Distribution of severity categories (none, mild, severe, very severe) at Week 12.
- RLS-6 Scales: patients' rating of severity of RLS and related features (change from baseline to week 12). The RLS-6 scales consist of six items of which four are related to severity of RLS and two are related to sleep and tiredness during the day.
- Clinical Global Impression (CGI) by the investigator: global ratings of illness, change in severity and therapeutic efficacy
- Clinical Global Impression for the treatment of RLS patients (CGI-RLS):
- Number of responders at Week 12 in two RLS-6 subscales ("severity during the night" and "severity during the daytime at rest"): responders defined as patients with a ≥ 50% improvement from baseline.

Outcomes and estimation
In the primary analysis all doses of Lisuride TDS showed statistically significant decreases in IRLS sum score compared to placebo, i.e. all 3 doses were superior over placebo (Table 2). Regarding the treatment effects, the two highest doses (5 mg and 10 mg) of Lisuride TDS were comparable and for both treatment arms the point estimate (-8.8 for Lisuride 10mg and -8.2 for Lisuride 5 mg) met the clinical relevance margin of an IRLS change of -6 points (established by the EURLSSG as a minimum requirement for clinical relevance compared to placebo).
Though the Lisuride TDS 2.5 mg dose was statistically significantly superior to placebo, its point estimate of -4.5 did not meet the clinical relevance margin. In summary, the primary efficacy analyses support Lisuride TDS 5 mg and 10 mg as statistically and clinically efficacious dose levels in contrast to 2.5mg which was statistically, but not clinically significantly superior to placebo. The results were supported by analyses on the PP set.

Table 2. IRLS Rating Scale sum scores – LS-Means compared to placebo (FAS with LOCF)

		Placebo	Lisuride 2.5 mg (10 cm^2)	Lisuride 5.0 mg (20 cm^2)	Lisuride 10 mg (40 cm^2)
	Statistic	N = 52	N = 52	N = 52	N = 50
Change from baseline to Week 12	LS-M	-8.2	-12.7	-16.3	-17.0
	97.5% CI	[-11.4; -4.9]	[-16.0; -9.4]	[-19.6; -13.1]	[-20.3; -13.7]
Difference active drug vs. placebo	LS-M	n.a.	-4.5	-8.2	-8.8
	97.5% CI	n.a.	[-∞; -0.5]	[-∞; -4.1]	[-∞; -4.8]
	p-value	n.a.	0.0139	< 0.0001	< 0.0001

Analyses on *responders on IRLS scores* showed statistically significant differences favouring lisuride over placebo in the Lisuride TDS 5mg and 10mg groups. The respective result of the Lisuride TDS 2.5mg group was statistically not significantly superior over placebo and was less favourable. The analysis on remitters was favourable for Lisuride TDS, but due to imbalances between the placebo and

the Lisuride TDS groups regarding the IRLS severity level at baseline (there were more patients on a very severe level in the placebo group) this should be interpreted with caution.

Secondary parameters overall were in line with results of the primary parameter, also indicating a dose dependent improvement with lisuride TDS, but lisuride TDS 10 mg performed only slightly better than Lisuride TDS 5 mg. For most secondary variables, the differences between Lisuride TDS 2.5 mg and placebo did not reach the level of statistical significance

A high number of patients did not complete the study. This was somewhat more pronounced in the 5.0 and 10.0 mg Lisuride TDS treatment groups (38.9% and 40% non-completers) than in the placebo and the 2.5mg Lisuride TDS group (each 32.1% non-completers). An increase of discontinuations due to adverse events with increasing dose of Lisuride TDS was shown (range 20.8% to 36% of patients). On the other hand the discontinuation rate due to lack of efficacy of the 2.5mg Lisuride TDS dose was quite similar to the placebo group (13.2 vs. 15.1%).

Overuse of patches was seen in both study periods and was comparable in the lisuride TDS groups and the placebo group (except for higher compliance in the 10 mg Lisuride TDS group), indicating an adhesiveness issue. The better results in the maintenance phase indicate that patients learned to fix the patches with an additional hypoallergenic tape. However, the 10mg Lisuride TDS group still showed a marked overuse of patches in the maintenance phase.

At the request of the CHMP, the applicant provided at Day 121 long term data for the open label period of TULIR 02/01. Patients who completed the double-blind (DB) period were in principal given the opportunity to participate in the OL period (single arm lisuride/stop of study medication after DB period for 0 to 7 days). A total of 128 of the 210 (60%) patients who were randomized to treatment in the core DB period continued treatment or started treatment (former placebo patients) with lisuride in the OL period (of note 135 patients completed the DB period of TULIR 02/01 and 125 completed without major protocol violations). Of these patients, 52.3% completed the OL period of the study (up to week 48), i.e. 31.9% of patients, who were randomized to treatment at baseline of the core DB period. The major reasons for discontinuations in the OL period (pooled for all dose levels of lisuride) were drug-related irritant skin reactions (26 %) and lack of efficacy (7.8%).This percentage is comparable to that of the DB period (25% and 7% respectively).
In summary, around two third of patients discontinued within 11 months. Up to week 100, only 20.3% of patients, who were randomized to treatment at baseline of the core DB period remained in the study.

The endpoint analysis using LOCF revealed a statistically and clinically significant improvement in the IRLS total score as change from DB baseline (-16.2 ± 11.1, [95% confidence interval (CI): -18.2; -14.2]; $p < 0.0001$). The mean change from BL-OL to the end of the OL period (LOCF) was smaller than that from BL-DB: -12.4 ± 10.5 (95% CI: -14.3; -10.5). The difference between the IRLS sum score at Visit 11 (LOCF) and BL-DB as well as BL-OL was statistically significant ($p < 0.0001$). However, it is to consider that BL-OL IRLS total score was rather high again, with a mean absolute value of 25.5 (± 7.2).

The majority of the patients improved in the IRLS severity category since DB baseline (83.2%, FAS-OL with LOCF) or did not change (14.4%). In the OL period between week 16 and week 48 twenty-nine (23.2%) patients improved and 45 (35%) remained unchanged. However, in 50 (40.0%) patients the IRLS total score worsened between Week 16 and 48.

In the long-term open-label periods of TULIR 02/01, the rate of clinically relevant augmentation was 7.0%. Median time to occurrence of augmentation was approximately one year, indicating that the risk of augmentation is increasing with exposure time to lisuride treatment.

At end of OL period (week 48/LOCF) mean dose was 6.4 mg lisuride, median dose was 7.5 mg. The maximum dose in the open label period was quite evenly distributed between 5.0, 7.5 and 10.0 mg lisuride. However, the 2.5 mg dose of lisuride was the maximum dose only in 10% of patients. This

indicates that the 2.5 mg lisuride dose is not effective in the majority of patients, as it was already seen in the core DB period.

A total of 60 patients entered the OL-extension period. Seventeen patients discontinued prematurely. In summary, less than a quarter of patients who were randomized to treatment at baseline of the core DB period remained in the study till Visit 13/week 100. The mean IRLS sum score of completers at Visit 13/week 100 was 10.4 (± 9.4). Of note, the population in the OL extension period was already a highly selected one, since only patients with preceding sufficient efficacy and no marked adverse events had the option to participate.

Thirty-five % of patients in the OL extension period, but interestingly only 5.6% in the OL period, had an overuse of patches of at least 20%, mainly due to patch adhesiveness issues.

- Main study

Study TULIR 03/01

METHODS

Study Participants
A total of 309 patients with moderate to severe RLS were randomized. Study participants had idiopathic or uremic (n= 3) restless legs syndrome. Diagnosis was based on the diagnostic criteria of the International Restless Legs Study Group (IRLSSG). Subjects had continuous and stable RLS symptoms during the last 4 weeks with an IRLS Rating Scale score ≥ 15 and RLS Diagnostic Index > 10 at baseline. The study population included those previously not treated for RLS (*de novo* patients) and those pre-treated but not well controlled with existing treatment, including those pre-treated with dopaminergic therapy.

Treatments
Placebo patches were first applied for at least 7 days during which, if necessary, previous treatment was also washed out. This was followed by 12 weeks of double-blind, double- dummy treatment. Individual dose adjustments always varying both the patches and the capsules in order to preserve the blind was performed during the first 8 weeks to find an individually optimal dose. Patients applied up to 2 patches (1 of 20 cm^2, 1 of 10 cm^2) of lisuride TDS or matching placebo every other day. Capsules containing the active comparator ropinirole tablets or matching placebo tablets were taken once daily. From week 8 till week 12 the dose was fixed at the individually determined optimal dose. A summary of study TULIR 03/01 is shown in Table 3.

Table 3. Summary of pivotal study in RLS TULIR 03/01

Study number	**Study design**	**Study and control drugs**	**Duration**	**Clinical endpoints**
TULIR 03/01 Pivotal efficacy trial	Double-blind, randomized, double-dummy, active- and placebo-controlled n=309 (randomized) n=300 (FAS) n=245 (PPS) n=197 (CS without major protocol violation) Males and females	lisuride TDS (individual optimized dose up to 30 cm^2) every 48h (n = 152) Oral ropinirole (up to 3 mg/day) daily (n = 78) Placebo (n = 79)	● 7 -10 days run-in /wash-out period ● 8 weeks dose adjustment ● 4 weeks maintenance period	Change of IRLS sum score from baseline to end of treatment Responder and remitter's analysis

		every 48h		

CS=completer set, PPS=per protocol set , FAS=full analysis set

Objectives

The primary study objective was three-fold: to investigate whether there is superior efficacy of an individually optimised dose of transdermal lisuride (dose range: 2.5 to 7.5 mg every second day) compared first to placebo, and secondly to an individually optimised dose of ropinirole (dose range: 1.0 to 3.0 mg/day) after 12 weeks. Thirdly, the objective was to investigate whether an optimised individual dose of Ropinirole (dose range: 1.0 to 3.0 mg / day) had superior efficacy compared to placebo for assessment of assay sensitivity.

Secondary study objectives were to evaluate and assess the quality of life, tolerability and safety of lisuride patch in comparison to placebo and ropinirole after 12 weeks of treatment.

Outcomes/endpoints

Primary clinical endpoint was the absolute change of the International Restless Legs Study Group Rating Scale (IRLS) total score from baseline till end-point at week 12. Clinical relevance was evaluated by responder and remitter's analysis. Responders were defined as subjects with a $\geq$ 50% improvement in IRLS total score. Remitters were defined as subjects with an IRLS score of 0 (Remitter-0) or patients with no or mild symptoms (Remitter-10).

Other secondary efficacy variables were defined and included: a) the frequency distribution of severity categories, change in sub-scores "symptom severity" and "symptom impact" using IRL, b) patients' severity rating using the Restless Legs Syndrome severity scale (RLS-6), c) the investigators' global ratings of illness, change in severity and therapeutic efficacy using the CGI and CGI – RLS scales.

Sample size

Based on data from TULIR 02/01, with an assumed $\alpha = 0.05$ (two sided), $\beta = 0.20$, a difference between lisuride and placebo of $\delta = 5.0$ IRLS units and a standard deviation for these difference of $\sigma =$ 10 units as well as a ratio of 2:1 (lisuride: placebo), 95 patients were randomised in the lisuride group and 48 in the ropinirole group.

Based on two pivotal Ropinirole placebo-controlled trials with an assumed $\alpha = 0.05$ (two sided), $\beta =$ 0.20, a difference between lisuride and ropinirole of $\delta = 4$ points and a standard deviation for this difference of $\sigma = 10$ points as well as a ratio of 2:1 (lisuride: ropinirole), 150 patients were to be randomised in the lisuride group and 75 in the ropinirole group. Using the same sample size in the placebo group as in the ropinirole group, a smallest difference between ropinirole and placebo of $\delta =$ 4.6 points, if actually existing, could be demonstrated.

From these considerations, with a ratio of 2:1:1 (lisuride : ropinirole : placebo) a total of 150 patients were expected in the Lisuride group and 75 patients each in the Ropinirole and the placebo groups. Thus, the total sample size was 300 patients and with the assumption that less than 10% of patients would drop out 320 patients were to be enrolled.

Randomisation

Randomisation was performed in blocks prior to the start of the studies. The patients were randomised in a ratio of 2:1:1 (lisuride: ropinirole: placebo) to the treatments in study TULIR 03/01. The randomised treatment period was double-blind.

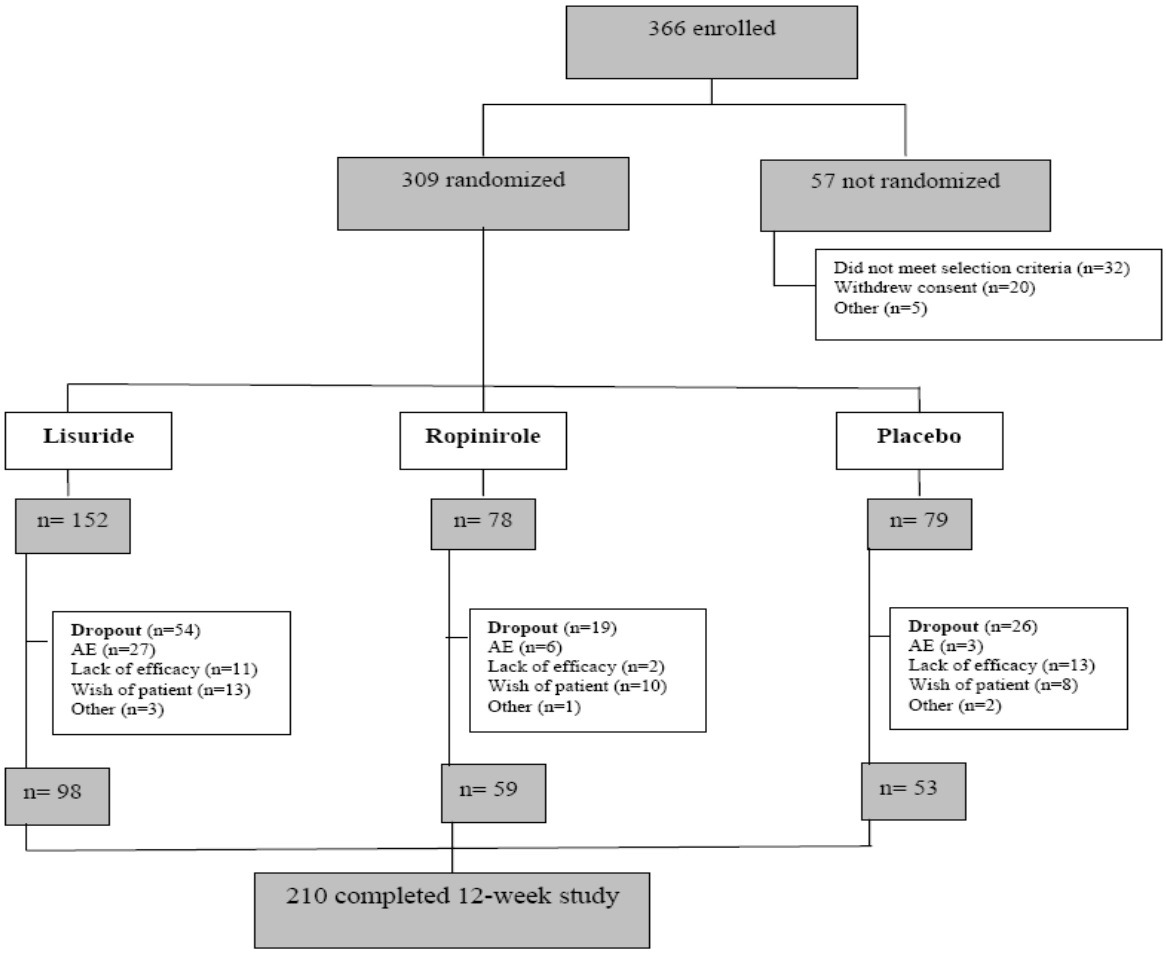
Blinding (masking)
A double-dummy design was used in this study in order to keep treatment blind. Each patient had to take ropinirole or matching placebo capsules every evening as well as to apply lisuride- or matching placebo patches every second morning. The double-blind aspect of this trial was maintained within each titration step.

Statistical methods
An ANCOVA model was used to analyse absolute change from baseline to the end of treatment in the IRLS total score. Dose/treatment-groups (as factor of interest) and baseline value (as covariate) were included in the model. Pair-wise comparisons were tested and corresponding confidence intervals were derived. A closed test procedure was performed with respect to the comparison of the study arms.
Each significance test (two sample one-sided t-test) was performed at the 2.5% level. The procedure was terminated when a null hypothesis could not be rejected. If it was found that the null hypothesis could not be rejected, no further confirmatory analysis was conducted, but the descriptive analysis (estimators, standard error, confidence intervals, p-value) were calculated for all hypotheses but were interpreted only in an exploratory manner. The analyses were performed for the FAS (Full Analysis Set) which is the primary analysis set, the PPS (Per Protocol Set) and the CS (Completer Set).

Results

Participant flow
Fig. 2 below illustrates the participant flow in study TULIR 03/01.

Fig. 2. Summary of subject disposition of study TULIR 03/01



Recruitment
Patients were recruited by neurologists in outpatient units of neurological hospital departments or from private practices specialized in sleep medicine. There were 37 centres (Germany 35, Austria 2) which recruited patients.

Conduct of the study
The median exposure to trial medication was 12 weeks. Due to dropouts, the average exposure time was about 70 days in all three treatment groups. In total, 72 major protocol violations were identified in 64 patients at baseline or during the study until Visit 7. Of these 64 patients, 28 patients were treated with lisuride (18.4 %), 22 with ropinirole (28.2 %) and 14 with placebo (17.7 %). The most frequently reported major protocol violation in approximately half of the patients was 'premature discontinuation with reasons other than adverse events or lack of efficacy' with 14 (9.2 %), 11 (14.1 %) and 9 (11.4 %) in the respective treatment group.
According to the blind review protocol 18 patients reported prohibited concomitant medication during the study.

Baseline data
All three treatment groups were well balanced with respect to demographic and most clinical characteristics. Mean age in the total FAS population was 58.6 years (range 24-80 years). All patients were Caucasians, 73.8 % were female. There were only 3 patients with uremic type of RLS. Mean (median) time since first diagnosis of RLS was 3.2 (1.9) years. Confirmation of RLS by

polysomnography was available for around 20 % of patients in all groups. A family history of RLS was present in 46.9 % of the patients. The mean IRLS Rating Scale total score was about 28, indicating severe disease. Most patients were treated with dopaminergic drugs prior to study start (80.3 % of total number of patients). Almost all of those had responded to prior dopaminergic RLS medication.

Numbers analysed

Table 4 below summarises the data sets analysed**.**

Table 4. Study TULIR 03/01. Summary of data sets analysed

	TULIR 03/01		
	Placebo	**Lisuride**	**Ropinirole**
Randomised	79 (100)	152 (100)	78 (100)
Full Analysis Set (FAS)	77 (97.5)	148 (97.4)	75 (96.2)
Per-protocol Set (PPS)	65 (82.3)	95 (62.5)	51 (65.4)
Completer set (CS)	51 (64.6)	95 (62.5)	51 (65.4)

Outcomes and estimation

The primary efficacy end-point was the absolute change of the IRLS sum score from baseline to the end of the double-blind period. The course of the IRLS scores is depicted in Figure 3 below. The summary for the mean values for baseline, end of maintenance period (week 12) and change from baseline to end of maintenance period; and comparison between the group differences are shown in Tables 5-7. Lower scores denote symptoms of lesser severity; negative changes indicate improvement in RLS symptoms. At baseline all treatment groups had similarly high IRLS ratings on average. The scores improved until end of the double-bind treatment in all groups, with largest improvement in the lisuride group, followed by the ropinirole group, and smallest improvement in the placebo group.

Figure 3. Course of IRLS scores during study TULIR 03/01 (FAS/LOCF)

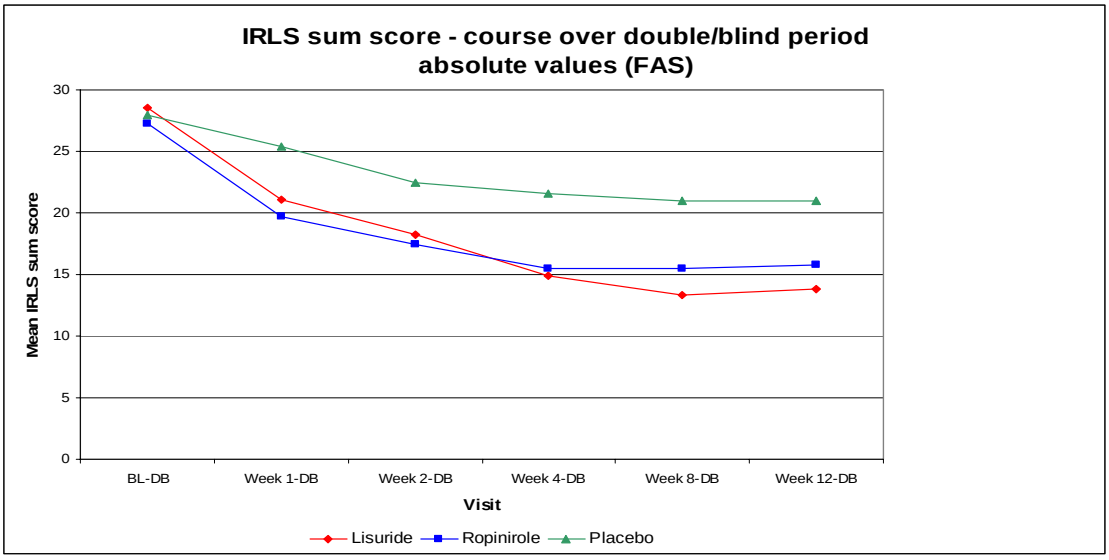


Table 5. IRLS Rating Sale total score: original values and change from baseline.

		Statistic	Lisuride N = 148	Ropinirole N = 75	Placebo N = 77
V 2/ Baseline		M ± SD	28.5 ± 5.9	27.3 ± 5.6	27.9 ± 6.1
		Median	29.0	28.0	29.0
		Range	15 – 39	15 – 38	15 – 38
V 7 / LOCF		M ± SD	13.8 ± 10.91	15.8 ± 9.46	21.0 ± 11.75
		Median	12.0	16.0	22.0
		Range	0 – 40	0 – 35	0 – 39
	Δ baseline	M ± SD	-14.6 ± 10.95	-11.6 ± 9.32	-6.9 ± 10.56
		Median	-16.0	-11.0	-6.0
		Range	-37 – 15	-32 – 8	-36 – 9

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum, RLS: 0: none, 1 – 10: mild, 11 – 20: moderate, 21 – 30: severe, 31 – 40: very severe

Table 6. IRLS Rating Scale sum scores: LS-means comparisons (FAS with LOCF)

	Statistic	Lisuride N = 148	Ropinirole N = 75	Placebo N = 77
EOT change from baseline (LOCF)	LS-Mean	-14.4	-11.9	-6.9
	97.5% CI	[-16.3;-12.6]	[-14.5;-9.2]	[-9.6;-4.3]
Difference Lisuride vs. Ropinirole and Placebo	LS-Mean	n.a.	-2.6	**-7.5**
	97.5% CI	n.a.	[-∞;0.3]	**[-∞;-4.7]**
	p-value	n.a.	0.0381	**< 0.0001**
Difference Ropinirole vs. Placebo	LS-Mean	n.a.	n.a.	-4.9
	97.5% CI	n.a.	n.a.	[-∞;-1.7]
	p-value	n.a.	n.a.	0.0015

Remarks: EOT: end of treatment (Week 12 or time of premature discontinuation), LS-Mean: Least square means as derived from an ANCOVA model with treatment as a fixed factor, baseline IRLS total score as a covariate, and changes in the IRLS total score from baseline to end of treatment. Larger negative values indicate larger improvements.
CI: confidence limits of LS-Mean, confidence limits for differences are **one-sided**
p-value: p-value for **one-sided** t-test of LS means differences
n.a.: not applicable

Table 7. IRLS Rating Scale sum scores: LS-means comparisons (Completer set)

	Statistic	Lisuride N = 95	Ropinirole N = 51	Placebo N = 51
EOT change from baseline (LOCF)	LS-Mean	-16.1	-12.5	-10.3
	97.5% CI	[-18.3;-13.9]	[-15.5;-9.5]	[-13.4;-7.3]
Difference Lisuride vs. Ropinirole and Placebo	LS-Mean	n.a.	-3.6	**-5.8**
	97.5% CI	n.a.	[-∞;-0.3]	**[-∞;-2.4]**
	p-value	n.a.	0.033	**0.001**
Difference Ropinirole vs. Placebo	LS-Mean	n.a.	n.a.	-2.2
	97.5% CI	n.a.	n.a.	[-∞; 1.6]
	p-value	n.a.	n.a.	0.257

Remarks: EOT: end of treatment week 12, LS-Mean: Least square means as derived from an ANCOVA model with treatment as a fixed factor, baseline IRLS total score as a covariate, and changes in the IRLS total score from endpoint of the maintenance phase (Week 12) to baseline. Larger negative values indicate larger improvements.
CI: confidence limits of LS-Mean, confidence limits for differences are **one-sided**
p-value: p-value for **one-sided** t-test of LS means differences
n.a.: not applicable

In this primary analysis Lisuride TDS showed statistically significant and clinically relevant superior efficacy over placebo in the ITT population (difference of -7.5 in the IRLS sum score, upper confidence limit -4.7; p<0.0001). However, Lisuride TDS missed statistical significant superiority over the active comparator ropinirole (point estimate -2.6, upper confidence limit 0.3; one-sided p-

value 0.0381), therefore confirmatory testing stopped. Theoretically, it cannot be precluded that lisuride TDS would have performed even inferior to ropinirole if up-titration to 4mg (as is acceptable according to the SPC of ropinirole) would have been permitted, since 33% of the ropinirole patients were on the highest permitted dose level (3mg) at end of treatment. This fact might have influenced the efficacy outcome in favour of Lisuride TDS in the comparisons of the two active treatments. Superior efficacy of ropinirole over placebo was shown on an exploratory level. The results in the primary analyses were supported by analyses on the PP set.

At the end of double-blind treatment, more responder and remitter-10 patients were observed in the lisuride TDS group than in both other groups. Lisuride TDS was superior to ropinirole in the responder rate (lisuride 56.1 % vs. ropinirole 41.3 %, p=0.0470, two-sided) and slightly more patients in the lisuride TDS than in the ropinirole group were classified as remitter-10 patients.

A major issue in the TULIR 03/01 study was the frequently inadequate patch adhesiveness. 57% of patients in the TULIR 03/01 OL period and 71% of lisuride patients in the according double-blind period rated patch adhesiveness as poor or moderate. Even more critical was the fact that patients were advised to apply a new patch in case a patch lost its adhesiveness (to exactly the same area to which the previous patch was affixed). Consequently, the average dose of Lisuride TDS was probably higher than reported in several patients. Furthermore it is to be expected that efficacy of Lisuride TDS will be reduced frequently due to this issue, since a post-hoc subgroup analysis of the OL period of TULIR 03/01 in order to investigate the relationship on patch adhesiveness and efficacy showed that patients with poor/moderate adhesiveness had markedly higher IRLS sum scores (as change from DB baseline) than patients with good/excellent adhesiveness (change from DB-baseline: poor/moderate: -12.3 ± 11.2 [95%-CI: -14.7; -10.0]; good/excellent: -17.7 ± 9.5 [95%-CI: -19.54; -15.81]), which indicates substantial impact of adhesiveness on efficacy.

As for TULIR 02/01 no data of the open-label extension of the study (week 13 to 48) were provided at the initial submission. During the assessment procedure, the applicant provided long term data of TULIR 03/01. After completion of the 12-week DB period in which treatment with the lisuride patch was compared to ropinirole capsules or placebo, all patients who completed the DB period without adverse events or other safety findings, that in the opinion of the investigator would prevent their continued participation, were offered the opportunity to receive treatment with an individually optimized dose of lisuride (maximum dose: 7.5 mg / 48 hours) for up to four years.
Patients started OL treatment on the morning of the final assessment of the DB period with one 10 cm² lisuride patch (2.5 mg). The dose of lisuride was increased in 2.5 mg increments within three weeks until the optimal dose for the individual patient was obtained and should remain on a stable dose after 4 weeks. Assessments were mandatory at the end of Week 16 (Visit 8), Week 24 (Visit 9), Week 36 (Visit 10), and Week 48 (Visit 11). Furthermore, measurement of lisuride plasma levels was conducted.
Of the 192 patients who entered, 103 (53.4%) completed the 36-week OL period. 46.6% of patients discontinued prematurely from the open label period. The major reasons for discontinuation were AEs (63 patients, 32.8%), followed by lack/loss of efficacy (including non-responder: 15, 7.8%) and wish of patient (withdrawal of consent, 10 patients, 5.2%). That means 71% of all patients who discontinued prematurely did this due to adverse events (mainly application site reactions). Altogether only 33% of randomized patients at double-blind baseline completed the core DB period and the open label period up to week 48. If looking only at patients who were randomized to lisuride treatment at DB baseline: 152 patients were randomized to lisuride at BL-DB period, 98 completed DB period, 86 patients entered OL period and 50 patients completed OL period.

The results from the descriptive analysis show a change from DB baseline in the IRLS total score to Visit 11 (week 48/LOCF) overall of -15.2 ± 10.6 (95%- Confidence Interval [CI]: -16.7; -13.7). However, change from OL Baseline to Visit 11 was only -2 ± 10.4 [95%-CI: -3.5; -0.5]). Additionally a slight increase (Δ BL-OL: 1.6 ± 10.3 [95%-CI: -0.6; 3.8]) in the IRLS total score was observed in patients treated with lisuride already in the DB period.
Furthermore, 41 patients (21.4%) experienced a worsening of symptoms (negative shift of IRLS category) between OL Baseline and week 48 (V11/LOCF).

At Visit 11 (week 48/LOCF) in total 13.7% of patients completing the study were on the 2.5mg, 44.1% on the 5.0mg and 42.2% on the 7.5mg dose level of lisuride, indicating that the 2.5 mg lisuride dose is not effective in the majority of patients, as it was already seen in the core DB periods of TULIR 03/01 and TULIR 02/01.

In the long-term open-label period of TULIR 03/01, the rate of clinically relevant augmentation was 1.0%. Median time to occurrence of augmentation was approximately one year, indicating that the risk of augmentation is increasing with exposure time to lisuride treatment. Additionally, the incidence of potential cases of augmentation was 2.6% of patients.

Ancillary analyses

Analysis performed across trials (pooled analyses and meta-analysis)
Not applicable.

Clinical studies in special populations
Not applicable.

2. Idiopathic Parkinson's disease in combination with l-dopa

Besides RLS, the applicant initially sought approval for the treatment of idiopathic Parkinson's disease with lisuride patches in combination with levodopa. The recommended starting dose is 5µg/h (patch 5 mg/20 cm^2) applied every other day which may be increased after two weeks to 10 µg/h every other day (two patches 5mg/20 cm^2). The Applicant submitted one pivotal study and two exploratory studies in PD patients with different stages of the disease.

- **Dose response studies**

No systematic dose-response studies were performed for the PD indication.

- **Main study**

TULIP IIb was a double-blind, randomized, multi-centre, placebo-controlled study in levodopa-treated patients with idiopathic Parkinson's disease. After randomization, patients received either TDS lisuride or matching TDS placebo: one patch (lisuride 5 mg or placebo) every other day during the first 2 weeks of the study, then 2 patches every other day for the next consecutive 12 weeks.
A total of 334 male and female patients were enrolled and randomised. Patients had idiopathic PD of at least 3 years duration characterised by motor fluctuations, with a minimum total daily "OFF-time" of at least 2 hours during the waking day or at least 6 hours accumulated over 3 consecutive days, despite optimised oral anti-Parkinson therapy; taking stable levodopa dosage (i.e., 3 to 10 doses of levodopa per 24 hours); and taking stable doses of all other anti-Parkinson drugs.
Patients were excluded in case of secondary parkinsonism, significant neurological symptoms that were not accounted for by PD, treatment with dopamine agonists during the 4 weeks prior to enrolment, history or presence of either dementia or epilepsy (or treatment with neuroleptics), and presence of major depression.

Patients were not allowed to take dopamine agonists within 4 weeks prior to study enrolment or during their participation in the study, with the exception of study drug. Patients were allowed to take anti-cholinergics, amantadine, COMT-inhibitors, MAO-B inhibitors, and other necessary concomitant therapies for their PD. The dosing of these concomitant medications must have been stable for a minimum of 4 weeks prior to study enrolment. A dose adjustment of concomitant anti-Parkinson medication was allowed if dopaminergic side effects occurred.

The primary outcome measure was the change in the duration of daily "OFF-time" from baseline to week 14. The secondary efficacy parameters included duration of daily "ON-time" from baseline to the final visit (without and with troublesome dyskinesias); change from baseline to week 2, - 4, - 8 and final visit in the scores of Unified Parkinson's Disease Rating Scale (UPDRS) section II (daily living

activities), section III (motor function) and combined II/III; final visit in UPDRS section IV A scores (dyskinesias due to therapy); change from baseline to final visit clinical global impression (CGI) part 1 and quality-of-life (EQ-5D).

The primary efficacy analysis was conducted for the full analysis population (FAS) and the per-protocol population set (PPS).

The baseline characteristics of the two treatment groups were well balanced.

The results of the primary and secondary efficacy analyses are presented in Table 8 below.

OFF hours decreased from 5.85 hours to 4.33 for the lisuride patch and from 5.72 to 5.49 for the placebo patch. The difference of 1.29 hrs was statistically significant ($CI_{95\%}$ -1.90 <> -0.68).

Table 8. Study TULIP IIb**.** Results main endpoints (FAS/LOCF).

(LS mean ± s.e.m.)	**Lisuride TDS** (n=166)	**Placebo TDS** (n=163)	**Difference ($CI_{95\%}$)**	**p-Value** (ANCOVA)
Primary efficacy end-point				
Baseline Daily 'OFF''-Time (hours)	5.85 ± 2.63	5.72 ± 2.24		
Change in 'OFF''-Time (hours)	-1.52 ± 0.26	-0.23 ± 0.26	-1.29 -1.90 ; -0.68	< 0.001
Secondary efficacy end-points				
Responder's analysis [A] (≥ 1 hr improvement)	94/166 57%	57/163 35%	21% 11% ; 32%	< 0.0001[B]
Total Daily 'On'-Time (hours)				
Without Troublesome Dyskinesias	1.26 ± 0.28	0.01 ± 0.28	1.25 ± 0.34	< 0.001
With Troublesome Dyskinesias	-0.01 ± 0.13	-0.04 ± 0.13	- 0.03 ± 0.15	0.854
Chance in UPDRS Score				
UPDRS II Baseline	13.5 ± 6.9	13.2 ± 6.9		
Change	-2.62 ± 0.38	-0.37 ± 0.38	-2.24 ± 0.40	<0.001
UPDRS III Baseline	28.1 ± 15.0	27.6 ± 15.4		
Change	-5.17 ± 0.68	-1.83 ± 0.68	-3.34 ± 0.81	<0.001
UPDRS IV (Complication of Therapy)				
Baseline	2.1 ± 2.4	1.9 ± 2.4		
Change	-0.27 ± 0.12	-0.06 ± 0.12	-0.21 ± 0.15	0.155

[A] Lisuride = 161; placebo=157; [B] Chi-square test
ANCOVA= analysis of covariance including treatment, country and the covariate baseline
A "responder" was defined as a patient who, from baseline to study endpoint, had an improvement of ≥ 1 hour during Off-time.

The applicant submitted the results for the TULIP IIb extension study during the assessment procedure. The objective of this study was to evaluate the long term outcome, efficacy, safety and local tolerability of lisuride TDS (2 x 20 cm^2 patches every 48 hrs). The extension study was to be nominally 34 weeks in duration.

Only 28 patients of the lisuride group from the original 166 patients could be recruited into this study. The study was only confined to some of the original countries. Furthermore, 4 patients from the original placebo group switched immediately to the lisuride group. Other patients could do this later, thus 5 patients switched during the study. Their baseline values were included in the placebo group, their final values in the lisuride group. The primary parameter of the original study, i.e. off time was not determined any more. For the UPDRS III and UPDR IV scores the original positive effects appeared maintained. Seven patients from the lisuride group discontinued the study (7 out of 32: 22%) due to local reactions.

- Other studies

Two small pilot studies have been performed: one in advanced (AXN081004CLI) and one in *de novo* (AXN081002CLI) Parkinson's disease (PD) patients. Although these studies were primarily conducted to investigate the pharmacokinetics and tolerability of TDS lisuride, some clinical efficacy end-points were also included.

Study AXN081004CLI was an open, single centre, exploratory pharmacokinetic and dose-finding study in elderly subjects with advanced PD (add-on to levodopa) despite optimized oral therapies. Treatment dose was a single patch (15 cm^2) and multiples up to 4 patches. Mobility score over the active day (self-rating of mobility every 30 minutes) was the main clinical efficacy variable.
An improvement in the number of switches within the motor scale was observed following treatment with TDS lisuride and an average decrease in mobility change over the first 3 days of treatment.

Study AXN081002CLI was an open, single centre, pharmacokinetic and dose-finding study in newly diagnosed PD patients. Treatment started with one 20 cm² TDS (5mcg/h) to be replaced every other day for up to 2 weeks with a subsequent doubling of the dose (2 patches every other evening) or, if necessary from a clinical point of view, even higher dosages to seven patches. Thereafter, treatment was continued with two patches changed every other day up to the end of the treatment. Motor function was assessed by taking the UPDRS III motor scores at baseline, at the time of blood samplings and the time of dose increase.
The UPDRS III score decreased by 31% compared to baseline. When the UPDRS III score was plotted against the plasma lisuride levels, a trend towards increased effect on motor score with increasing systemic availability of lisuride was noted.

3. Parenteral therapy of advanced idiopathic Parkinson's disease

The initial application included lisuride 2.0 mg powder for solution for infusion which was intended to be administered as a subcutaneous infusion in advanced idiopathic Parkinson's disease. The dose should be titrated on an individual basis starting with 25 mcg/h which was gradually increased up to 160 mcg/h depending on the observed effect and tolerability. The daily dose should not exceed 2.0 mg. In general, lisuride was to be administered during the waking hours, but it might be given overnight in case of night time motor complications.
The package submitted included four controlled studies i.e. the CALIPSO study, Studies R0002 (Stocchi 2002), Study R87178 (based on a publication by Baronti et al. 1992) and a study by Stocchi 1993. In addition several uncontrolled studies were submitted as supportive evidence.

Dose response studies

There were no dose response studies.

Main study

The CALIPSO study was a randomised, multicentre, controlled, parallel group study. Patients included suffered from Parkinson's disease with motor complications with a poor response to oral therapy. Patients were randomised to subcutaneous infusion of either lisuride (n=31) or placebo infusion (N=32). A double-dummy technique was used. Treatment was added to L-dopa. Oral

dopamine agonists were replaced by placebo for patients receiving the lisuride infusion and continued for the placebo infusion group. Patients were titrated to their individual optimal infusion rate over a week on an in-patient basis. There was an option for continuing in an open label extension study.

The device was a portable minipump. Prior to infusion, patients received oral domperidone to prevent dopaminergic side effects. Treatment duration was 6 weeks during which infusion rate could be adapted.

The titration schedule was 25 mcg /h. The dose was slowly increased in steps of 5-10 mcg/h depending on the therapeutic effect and tolerance. The maximum infusion volume per day was limited to 1.25 ml on the first day and maximum daily increments of 1.25 ml in subsequent days. The maximum of 5 ml allowed could be reached within four days (equal to 2.0 mg lisuride). The infusion was applied at daytime up to 16 hours.

The study was a superiority study aimed to show superior efficacy of subcutaneously applied lisuride continuous infusion as add-on medication in levodopa-treated patients with Parkinson's disease and motor complications with no or poor response to standard therapy compared to standard L-dopa-dopamine-agonists combination.

Primary endpoint was the change in total daily "OFF-time and ON-time with troublesome dyskinesias" at the end of study. Secondary endpoints included other ON/OFF based variables, UPDRS derived variables and CGI based variables.

The primary analysis data set was the ITT population defined by the Applicant as all patients randomised and who received one dose of study medication and for whom efficacy data were available at baseline and post baseline. The Last Observation Carried Forward was used in order to deal with missing values.

Primary comparison was the comparison of change in "OFF-time and ON-time with troublesome dyskinesias" between baseline and end of study.
One amendment concerned the introduction of responder criteria to further explore the clinically relevance of potential differences between lisuride and placebo. A new CGI responder criterion was introduced during the data analysis when it became obvious that many patients in the placebo group showed "'minimally" improvement. This new responder criterion involved only patients with a "very much" or "much" improvement in the CGI item 2.

Major outcome variables are presented in table 9. Responders were defined as a subject who had an improvement by at least 30% in the primary efficacy measure as well as in duration of daily "OFF-time" and "ON-time without troublesome dyskinesias". Results were similar for the per protocol and completers set. HR quality of life did not change.

Table 9. CALIPSO study. Major outcome variables

n-ITT	**Lisuride** 31		**Placebo** 32				
Primary endpoint ON-Off with troublesome dyskinesias							
Baseline (hr, mean, sd)	9.8 (4.1)		9.8 (3.3)		Diff.	$CI_{95\%}$	p-value
$Change_{End\ of\ study}$ (mean , sd)[A]	**-2.90 (5.9)**		**-1.27 (4.8)**		**-1.63**	**-3.79 <> 0.52**	**0.13[$]**
Secondary endpoints							
OFF-time (hrs)	-1.06		+0.26		-1.31	-3.44 <> 0.81	0.22
ON with troublesome dyskinesias (hrs)	-1.85		-1.52		-0.33	-1.88 <> 1.21	0.67
ON-time(hrs)	+2.20		+1.23		0.97	-1.09 <> 3.04	0.35
Sleep time(hrs)	+0.75		-0.01		0.75	-0.11 <> 1.62	0.08
UPDRS total score	-8.97		-4.07		1.90	-12.3 <> 2.5	0.19
$Responders_{ITT}$	61%		41%				0.13[#]
$Responders_{PPP}$	65%		41%				0.07[#]
$Responders_{Completers}$	70%		38.5%				0.05[#]
CGI							
Very much improved	6.9		6.7		Overall p=0.0014[##]		
Much improved	41.4	48.3	6.7	13.3	Difference in > much improved p=0.0048[#]		
Minimally improved	20.7		40.0				
Unchanged	20.7		20.0				
Minimally worse	3.4		26.7				
Much worse	6.9		0.0				

[A]End of study = value at week 6 or LOCF value.
[$]ANCOVA=analysis of covariance with treatment as main factor and baseline diary values as covariate, last observation carried forward, LS: least square,
[#] Fisher's exact test, [##] Mann Whitney U-test

Supportive studies

In Stocchi et al. (2002), 40 patients were either treated with levodopa (n=20) plus any other anti-Parkinson treatment considered necessary or levodopa plus s.c. lisuride (n=20) for 4 years. Lisuride infusion led to a reduction in the levodopa dose and a significant improvement of motor fluctuations. However, this study was not blinded, therefore diaries made by the patients may be heavily biased. Furthermore since no placebo infusions were included it is not clear how much of this effect was due to placebo (in the CALIPSO study placebo infusion had a significant effect). Furthermore, the study did not answer the question whether lisuride infusion can improve motor conditions as well or better than an optimized oral therapy. The same applied to the study of Stocchi et al., 1993, with 20 patients and for Baronti et al., 1992, for only 7 patients.

- **Discussion on clinical efficacy**

1. Restless Legs Syndrome

For the indication restless legs syndrome, the efficacy and safety of lisuride TDS has been investigated in one dose finding trial, TULIR 02/01, and one pivotal phase III trial, TULIR 03/01. The submitted data from these trials support short-term efficacy of Lisuride TDS 5 mg and 10 mg. However, since RLS is a chronic, even life-long disease, robust long-term efficacy data are essential. Due to the very high rate of discontinuations in all periods of the RLS trials (lisuride only: 32-40% dose dependently in DB period of TULIR 02/01, 47% OL period TULIR 02/01, 37% DB period TULIR 03/01 and 47% OL period TULIR 03/01), and the fact that the data from the open label extension trials were uncontrolled, there is not sufficient evidence for maintenance of efficacy

In study TULIR 03/01, lisuride TDS was numerically superior over ropinirole with regard to the primary efficacy parameter IRLS. However, this result should be interpreted with caution, as the ropinirole doses used in this study were probably sub-optimal.

The inadequate patch adhesiveness in the trials was a major concern. There were 71 % of patients in the double/blind period of study TULIR03/01, and 57 % in the subsequent open-label period that rated patch adhesiveness as poor or moderate. Data from the TULIR 03/01 study indicated that reduced patch adhesiveness was associated with reduced efficacy.

The premature discontinuation rates were very high in the pivotal RLS trials, mainly due to drug related irritant skin reactions. Approximately 2/3 of included patients of both trials discontinued prematurely between baseline of the double blind periods and week 48. When looking only at patients randomized to lisuride treatment already at double-blind baseline of TULIR 03/01, this number remained the same: only 33% of lisuride patients completed the core double-blind period and the open label period up to week 48. The very high rate of premature discontinuations in the clinical studies due to drug-related irritant skin reactions indicates that lisuride transdermal patch as it was studied in the present application is not suitable for use in clinical practice.

2. Treatment of idiopathic Parkinson's disease in combination with levodopa

The TULIP IIb study demonstrated that Lisuride TDS had a statistically significant effect vs. placebo in reducing OFF time in patients under basal levodopa therapy. However, the magnitude of the effect size was limited. No systematic dose-response studies were performed for the PD indication and the basis for the chosen dose in study TULIP IIb is therefore not clear.

The pivotal study was only 14 weeks, and this was considered too short to establish the long term safety and efficacy of lisuride TDS. The extension study could not overcome these shortcomings.

The high incidence of local skin reactions was a major problem. During the controlled phase of study TULIP IIb, 36.4% of the lisuride group had a local site reaction and 12% of the lisuride group dropped out due to such problems. During the extension phase 22% (7 out of 32) dropped out and at the end of the study, of the remaining patients, 21.6% had still strong to very strong reactions.
Only a few patients of the controlled phase (n=168) could be recommitted into the extended phase (n=28). Due to the high incidence of local application site reactions, the CHMP considered lisuride transdermal patch as it was studied in the present application as unsuitable for the long term treatment of PD.

The safety database was limited and did not allow estimates of rarer adverse events. The CHMP considered the limited size of the database to be a major issue.

Due to major objections on clinical efficacy, the applicant decided to withdraw the application for treatment of Parkinson's disease with lisuride TDS during the procedure.

3. Parenteral therapy of advanced idiopathic Parkinson's disease

During the procedure, the CHMP expressed its view that for a chronic therapy with subcutaneous administration, it is essential to demonstrate that it is superior to an oral therapy which is much less of a burden and of a risk for the patient. The pivotal CALIPSO study, which lasted only for 6 weeks (instead of the recommended 12 weeks), failed to achieve this goal. The extension study was without comparator and thus only demonstrating some maintenance of effects. Since the pivotal study failed to provide unequivocal results, the quality and the outcome of supporting studies would be of great importance. However, the design of these studies was different and therefore did not really support the data of the CALIPSO trial or the primary objective of this dossier i.e. to demonstrate superiority of subcutaneously administered lisuride versus optimized oral therapy

The most frequently reported adverse events in the CALIPSO trial were hallucinations (5 of 33 patients in the lisuride group, i.e. 15%, vs. only 1 patient in the placebo group) and gastrointestinal disturbances. Concern was expressed over the application site reactions with a high incidence of "nodules".

In the absence of the efficacy required for a subcutaneous infusion, and with a relatively unfavourable safety profile with a significant risk of hallucinations and application site reactions, the CHMP considered that the overall benefit/risk balance for Nenad subcutaneous infusion was negative.

Based on information received from the applicant during the procedure, the applicant decided not to pursue the MAA for Nenad subcutaneous infusion and the application for Nenad subcutaneous infusion was withdrawn.

Clinical safety

During the procedure the applicant modified the claimed indication, and the application for Parkinson's disease (PD) was withdrawn. The applicant refers, however, to safety data from the trials in PD in an integrated safety database, and the safety data for lisuride TDS in PD will therefore also be briefly discussed.
Lisuride is a dopamine agonist, and many of the adverse events observed in the main studies (e.g. dyskinesias in PD, somnolence, nausea, dizziness, visual hallucinations, insomnia, orthostatic hypotension, depression, hyperhidrosis) are associated with dopamine agonists in general.

- Patient exposure

Restless legs syndrome/lisuride transdermal system (TDS)
In TULIR 01/01 10 patients received 1 patch and 7 patients received 2 patches for a maximum of 3 weeks. In TULIR 02/01 53 patients received a Lisuride 2.5 mg (= 10 cm^2) patch for a mean duration of 74.1 ± 30.4 days, 54 patients received a Lisuride 5 mg (= 20 cm^2) patch for a mean duration of 74.4 ± 28.0 days and 50 patients received a Lisuride 10 mg (= 40 cm^2) patch for a mean duration of 74.9 ± 27.8 days. In TULIR 03/01 152 patients received a Lisuride 10 mg (= 40 cm^2) patch for a mean duration of 69.2 ± 25.4 days. In total 309 restless leg patients were treated with lisuride, with treatment durations up to 15 weeks.
In addition, 107 healthy subjects have been exposed by the lisuride transdermal route; treatment durations were generally limited to single doses or short periods.

Parkinson's disease /lisuride TDS
In the pivotal trial TULIP IIb for the indication Parkinson's disease, 168 patients were exposed to lisuride in the TDS route, with maximal provided treatment duration of 12 weeks.

- Adverse events

Dose-related adverse events (only studied for the TDS formulation in RLS patients) included dizziness, nasopharyngitis, night sweats, malaise, swelling and insomnia. Serious events included systemic adverse events only, mainly hallucinations, orthostatic hypotension and some nausea, which

are expected for a dopamine agonist. Psychiatric disorders (which can be expected from a dopamine agonist) and cardiovascular disorders, for which reports besides orthostatic hypotension (such as angina pectoris, peripheral oedema, hypertension, tachycardia) have been observed scattered over the indications were not discussed separately by the applicant.

Restless legs syndrome / TDS
As representative example for the application site and general AE frequency in the RLS indication, data from the TULIR 02/01 are presented in Tables 10, 11 and 12 below.

Table 10. Study TULIR 02/01 in RLS. Adverse events during treatment with drug relationship by system organ class and preferred term (≥ 3 patients affected per AE) (SAF)

	Placebo N=53		Lisuride 2.5 mg (10cm²) N=53		Lisuride 5 mg (20cm²) N=54		Lisurde 10 mg (40cm²) N=50	
	any	related	any	related	any	related	any	related
All system organ classes - N° of patients with AEs	45 (84.9)	*32 (60.4)*	44 (83.0)	*43 (81.1)*	52 (96.3)	*44 (81.5)*	46 (92.0)	*43 (86.0)*
Total N° of AEs	102	*60*	168	*114*	195	*134*	166	*121*
Skin and subcutaneous tissue disorders (total)	24 (45.3)	*23 (23.4)*	37 (69.8)	*37 (69.8)*	37 (68.5)	*36 (66.7)*	40 (80.0)	*40 (80.0)*
- Pruritus[(1)]	1 (1.9)	*1 (1.9)*	8 (15.1)	*8 (15.1)*	6 (11.1)	*6 (11.1)*	3 (6.0)	*3 (6.0)*
- Erythema[(1)]	5 (9.4)	*5 (9.4)*	7 (13.2)	*7 (13.2)*	4 (7.4)	*4(7.4)*	5 (10.0)	*5 (10.0)*
- Pruritus	9 (17.0)	*9 (17.0)*	17 (32.1)	*17 (32.1)*	19 (35.2)	*19 (35.2)*	24 (48.0)	*24 (48.0)*
- Rash erythematous	8 (15.1)	*7 (13.2)*	17 (32.1)	*17 (32.1)*	18 (33.3)	*17 (31.5)*	22 (44.0)	*22 (44.0)*
- Erythema	6 (11.3)	*6 (11.3)*	12 (22.6)	*12 (22.6)*	13 (24.1)	*13 (24.1)*	11 (22.0)	*10 (20.0)*
- Hyperhidrosis	1 (1.9)	*1 (1.9)*	1 (1.9)	*1 (1.9)*	3 (5.6)	*2 (3.7)*	1 (2.0)	*1 (2.0)*
Nervous system disorders (total)	23 (43.4)	*4 (7.5)*	26 (49.1)	*10 (18.9)*	26 (28.1)	*10 (18.5)*	21 (42.0)	*8 (16.0)*
- Headache	21 (39.6)	*4(7.5)*	25 (47.2)	*9 (17.0)*	23 (42.6)	*9 (16.7)*	17 (34.0)	*3 (6.0)*
- Dizziness	2 (3.8)	*1 (1.9)*	1 (1.9)	*1 (1.9)*	5 (9.3)	*3 (5.6)*	5(10.0)	*4 (8.0)*
Gastrointestinal disorders (total)	13 (24.5)	*7 (13.2)*	18 (34.0)	*15 (28.3)*	23 (42.6)	*17 (31.5)*	13 (26.0)	*10 (20.)*
- Nausea	7 (13.2)	*4 (6.7)*	15 (28.3)	*14 (26.4)*	10 (18.5)	*10 (18.5)*	12 (24.0)	*10 (20.0)*
- Vomiting	3 (5.7)	*2 (3.8)*	2 (3.8)	*1 (1.9)*	7 (13.0)	*6 (11.1)*	6 (12.0)	*4 (8.0)*
- Constipation	1 (1.9)	*1 (1.9)*	3 (5.7)	*3 (5.7)*	3 (5.6)	*1 (1.9)*	1 (2.0)	*1 (2.0)*
- Diarrhea	4 (7.5)	*3 (5.7)*	2 (3.8)	*1 (1.9)*	2 (3.7)	*1 (1.9)*	--	--
- Dry mouth	--	--	--	--	3 (5.6)	*2 (3.7)*	--	--
General disorders	--	--	6 (11.3)	*3 (5.7)*	8 (14.8)	*6 (11.1)*	4 (8.0)	*3 (6.0)*
- Fatigue	--	--	3 (5.7)	*3 (5.7)*	4 (7.4)	*2 (3.7)*	1 (2.0)	---
Ear and labyrinth disorders	4 (7.5)	*2 (3.8)*	3 (5.7)	*2 (3.8)*	5 (9.3)	*4 (7.4)*	4 (8.0)	*3 (6.0)*
- Vertigo	3 (5.7)	*1(1.9)*	2 (3.8)	*1 (1.9)*	5 (9.3)	*4 (7.4)*	4 (8.0)	*3 (6.0)*
Psychiatric disorders	3 (5.7)	*3 (5.7)*	6 (11.3)	*3 (5.7)*	6 (11.1)	*1 (1.9)*	8 (16.0)	*3 (6.0)*
- Sleep disorder	1 (1.9)	*1 (1.9)*	--	--	3 (5.6)	--	2 (4.0)	*1(2.0)*
- Insomnia	1 (1.9)	*1 (1.9)*	--	--	1 (1.9)	*1(1.9)*	3 (6.0)	*2 (4.0)*
Vascular disorders	2 (3.8)	*2 (3.8)*	2 (3.8)	--	6 (11.1)	*5 (9.3)*	4 (8.0)	*3 (6.0)*
Cardiac Disorders	2 (3.8)	--	--	--	3 (5.6)	*1 (1.9)*	--	--
Eye Disorders	1 (1.9)	*1 (1.9)*	--	--	3 (5.6)	*2 (3.7)*	1 (2.0)	--
Injury, poisoning & Procedural complication	--	--	1 (1.9)	--	1 (1.9)	--	3 (6.0)	*1 (2.0)*
Musculoskeletal & connective tissue disorders	5 (9.4)	--	8 (15.1)	--	8 (14.8)	*2 (3.7)*	5 (10.0)	--
- Back pain	3 (5.7)	--	4 (7.5)	--	2 (3.7)	--	3 (6.0)	--
Infections and infestations	4 (7.5)	---	8 (15.1)	*1 (1.9)*	7 (13.0)	--	6 (12.0)	*1 (2.0)*
- Nasopharyngitis	2 (3.8)	---	2 (3.8)	---	3 (5.6)	--	3 (6.0)	--
Respiratory, thoracic and mediastinal disorders	--	--	4 (7.5)	*1 (1.9)*	3 (5.6)	*1 (1.9)*	1 (2.0)	*1 (2.0)*

Remarks: SOCs listed are the same as in Table 12-6. and Table 12-7. Number of patients, percentage related to total number of patients per treatment group (in parentheses).
[(1)]Pruritus and erythema reported as application site reaction.
The groups refer to treatment during double-blind period. AEs are sorted by total number of events (any).
Drug relationship: possibly, probably, and definitely related to trial medication
Reference: Appendix 16.2, Table 302 and 305

Table 11. Study TULIR 02/01 in RLS. Treatment-related application site reactions and other skin reactions not specified as application site (patients who received at least one dose of study drug**)**

Application site:							
	N	Erythema	Reac-tion	Pruritus	Edema	Dermatitis	Total
2.5mg	53	7 (13.2%)	0	8 (15.1%)	0	0	15 **(28.3%)**
5mg	54	4 (7.4%)	0	6 (11.1%)	1 (1.9%)	0	11 **(20.4%)**
10mg	50	5 (10.0%)	0	3 (6.0%)	2 (4.0%)	0	10 **(20.0%)**
Placebo	53	5 (9.4%)	0	1 (1.9%)	0	1 (1.9%)	7 **(13.2%)**

Treatment related Erythema, Pruritus, Skin Swelling and Dermatitis - Not Specified as Application Site							
	N	Erythema		Pruritus **a)**	Skin Swelling	Dermatitis **b)**	Total
2.5mg	53	12 (22.6%)		17 (32.1%)	1 (1.9%)	0	30 **(56.1%)**
5mg	54	13 (24.1 %)		19 (35.2%)	0	0	32 **(59.3%)**
10mg	50	10 (20.0%)		24 (48.0%)	0	1 (2.0%)	35 **(70.0%)**
Placebo	53	6 (11.3%)		9 (17.0%)	0	0	15 **(28.3%)**

a) pruritus or pruritus generalized;
b) dermatitis or dermatitis allergic

Table 12. Study TULIR 02/01 in RLS. Application site assessment: relationship to patch administration (SAF with LOCF)

	Placebo	Lisuride 2.5 mg (10cm²)	Lisuride 5.0 mg (20cm²)	Lisuride 10 mg (40cm²)
Rash erythematous	**N = 53**	**N = 52**	**N = 54**	**N = 50**
V3 / Week 1 – TP	2 (3.8)	6 (11.3)	6 (11.1)	4 (8.0)
V4 / Week 4 – MP	8 (15.1)	11 (20.8)	12 (22.2)	12 (24.0)
V5 / Week 8- MP	10 (18.9)	22 (41.5)	18 (33.3)	25 (50.0)
V6 / Week 12 - MP	13 (24.5)	27 (50.9)	24 (44.4)	30 (60.0)
V7 / Week 13 – TA	8 (15.1)	20 (37.7)	15 (27.8)	17 (34.0)
Pruritus				
V3 / Week 1 – TP	2 (3.8)	6 (11.3)	4 (7.4)	1 (2.0)
V4 / Week 4 - MP	5 (9.4)	9 (17.0)	10 (18.5)	7 (14.0)
V5 / Week 8- MP	5 (9.4)	14 (26.4)	14 (25.9)	16 (32.0)
V6 / Week 12 - MP	8 (15.1)	19 (35.8)	20 (37.0)	22 (44.0)
V7 / Week 13 – TA	5 (9.4)	13 (24.5)	11 (20.4)	11 (22.0)
Sweating increased				
V3 / Week 1 – TP	--	--	--	--
V4 / Week 4 - MP	--	--	--	--
V5 / Week 8- MP	1 (1.9)	1 (1.9)	2 (3.7)	--
V6 / Week 12 - MP	--	1 (1.9)	1 (1.9)	1 (2.0)
V7 / Week 13 – TA	--	--	--	--

Remarks: The table gives number and percent (in parentheses) of patients.
TP: Titration phase, MP: Maintenance phase, TA: Taper phase
Last observation carried forward (LOCF) method was used in patients with premature discontinuation from the study.
Reference: Appendix 16.2, Table 337 (Rash erythematous), 338 (Pruritus), and 339 (sweating increased)

The main safety issue during the treatment with Lisuride TDS in RLS were skin reactions. There was a markedly higher rate of skin and subcutaneous tissue disorders (application site reactions and other skin reactions) in Lisuride TDS treated RLS patients (66.7%-80% in TULIR 02/01 and in TULIR 03/01 at least 45% of patients had application site reactions, 7.2% drug related skin disorders and 39.5% so-called other drug related skin reactions) compared to patients treated with placebo patches (23.4% in TULIR 02/01 as well as 10.2%/placebo patients and 15.4%/ropinirole patients in TULIR 03/01) indicating significant local tolerance issues especially due to the active pharmaceutical ingredient lisuride.

At the request of the CHMP, the applicant submitted safety data from the open label (OL) and OL extension studies of TULIR 02/01 and TULIR03/01 during the assessment procedure.

In study TULIR 02/01, a total of 66.4% of patients in the OL period experienced one or more newly occurred drug related adverse events, mainly various forms of skin reactions (around 60 % of patients in the OL period). Furthermore 39.1% of patients in the OL period and 36.7% had drug related adverse events ongoing from previous study period(s), again mainly application site reactions.

In summary, during the OL period 32.8% of patients had ongoing application site (AS) reactions, 55.5% had new AS reactions and 5.5% other drug related skin reactions. 14.1% of patients had severe AS reactions.
The number of patients with tolerability problems (CGI Item 4/AEs with significant interference on daytime activities or outweighing efficacy) was about 29% at the end of the OL period (V 11/LOCF).
The provided data showed that application site reactions were often recurring (many events) and were often persisting for a long time. Furthermore, as in the DB period, again a marked increase in number and severity of application site reactions with increasing dose was shown.

During the OL extension period around 36% of patients had ongoing AS reactions, 26% had new AS reactions and 3.3% other drug related skin reactions. 8.3% of patients discontinued due to AS reactions. Of note, also in the open label and the open label extension period 16.4% of patients used dermatological preparations of corticosteroids and further 5.5% antipruritic medications.

In the open label period of TULIR 03/01, the main reported adverse events were application site reactions (35.9 %), gastrointestinal disorders (13.5%), infections and infestations (13 %) and nervous

system disorders (12 %). During OL period, 49.5% patients had drug related newly occurred and 25.5% of patients ongoing drug related AEs from the DB period.

35.9% of patients reported one or more newly occurred application site reactions and 5.2 % reported newly occurred other skin reactions in the open label period (such as pruritus, generalized pruritus and skin exfoliation). 2.6 % of patients had application site reactions and 4.2 % other skin reactions/disorders on-going from DB period.
The number of patients reporting application site reactions increased markedly with increasing lisuride dose (patch area), from 8% of patients at the 2.5 mg dose level up to 32.3% of patients at the 7.5 mg dose level of lisuride. When pooled over all dose groups, there were 6.3% of patients with mild, 15.6% of patients with moderate and 14.1% of patients with severe application site reactions. Also the severity of drug related AEs (mainly AS reactions) increased markedly with increasing lisuride dose.

Furthermore, in the open label period 7.8% of patients used dermatological preparations of corticosteroids and further 3.1% patients antihistamines (local and systemic). Presumably the number of application site reactions would have been even higher without these concomitant medications.

Systemic drug-related AEs were those expected in the treatment with stimulation of dopamine receptors and were already known side effects of oral Lisuride (including headache, nausea, vomiting, dizziness, fatigue, vertigo, orthostatic hypotension). In TULIR 03/01 systemic side effects occurred more frequently in the ropinirole group. Especially nausea occurred more frequently under ropinirole (35.9%) than under lisuride (19.7%) or placebo (6.3%). In summary drug-related systemic AEs occurred in 39.5% of the lisuride TDS patients, 57.8% of the ropinirole patients and in 39.2% of the placebo patients. Of note, if there were early side effects typical for dopamine agonists (such as nausea or emesis), domperidone or metoclopramide could be given to alleviate/prevent such symptoms in the RLS trials. Altogether 14 patients (9.46%) in the lisuride group, 12 patients (16%) in the ropinirole group and 2 patients (2.6%) in the placebo group used one of the two drugs.

Parkinson's disease / TDS

The most frequently reported adverse events in study TULIP IIb were local reactions at the application site. Taking together the different sub-entities, such skin reactions add up to 61 of 168 patients. This means that they occurred in 36.3 % of the patients, in contrast to only 8 (4.8%) of the placebo group. However, when also including rarer local adverse events (i.e. occurrence in less than 3% of the patients), the frequency of application site reactions rises to 42%. Moreover, concerns remain to what extent application site reactions were recognized as such, if delayed in onset. The proportion of patients having erythema at the patch application site increased consistently from visit to visit over the course of the study.
Other AEs included psychiatric disorders; the most frequently reported being hallucinations (9/168). Further psychiatric AEs were insomnia, abnormal dreams, confused state and others. In total 11% of patients showed psychiatric symptoms (compared to 6% in the placebo group).
Also frequently reported were nausea and orthostatic hypotension.

The frequency of AEs of the lisuride patch and placebo-patch treatment in Parkinson's disease patients in Study Tulip IIb is summarized in table 13 below.

Table 13. Incidence of frequently reported adverse events, lisuride TDS, Parkinson's disease – TULIP IIb

MEDRA SOC **Preferred term**	**No of patients**	
	Lisuride	**Placebo**
N	**168**	**165**
Administration site conditions		
Application site erythema	**47**	**7**
Application site reaction	**9**	**1**
Application site dermatitis	**5**	**0**
Nervous system disorders		
Dyskinesia	**12**	**5**
Somnolence	**6**	**3**
Headache	**5**	**5**
Dizziness	**1**	**5**
Psychiatric disorders		
Hallucination	**5**	**2**
Gastrointestinal disorders		
Nausea	**6**	**7**
Musculoskeletal and connective tissue disorders		
Back pain	**4**	**6**

Frequently reported: ≥3% of patients in any group, irrespective of causality

- Serious adverse event/deaths/other significant events

Restless legs syndrome / TDS
In TULIR 01/01 no SAEs were reported. In TULIR 02/01 there were five patients with SAEs. Three of these (one in the 5mg and two in the 10mg Lisuride group) were drug-related orthostatic hypotensions. In TULIR 03/01 three patients from the lisuride group had SAEs (hypotension, diarrhea and acute renal failure), one of which was regarded to be drug related (hypotension/2.5 mg Lisuride TDS dose group). No deaths occurred in the TULIR trials. None of the local reactions observed in the patch studies were recorded as serious.

Parkinson's disease / TDS
In TULIP IIb 7/168 patients had SAEs (compared to 18/165 in the placebo group). Two deaths were reported: one from myocardial infarction in the placebo group, one from Non-Hodgkin's lymphoma in the lisuride group. For most of the SAEs a relationship with lisuride can not be excluded, but most appear unrelated.

- Laboratory findings

Only few patients showed clinically meaningful changes in laboratory values. Lisuride may cause liver enzymes increments, anemia (decreased Hb), and uremia. However, full sets of laboratory parameters were not provided for all trials. Sporadic changes in iron and ferritin in TULIR patients might indicate secondary causes of RLS, taking into account inclusion of around 20% de novo patients.
Laboratory data from patients with kidney or liver disease were not provided separately.
No cases of QTc prolongation, valvulopathy or fibrosis, or compulsive behaviour were reported in the trials. However, concerning detection of potential signs of fibrosis, the conducted studies were clearly too short, and therefore no conclusions can be drawn.

- Safety in special populations

No comprehensive information or formal analyses with regard to gender, age-dependence (including elderly and children), weight or pregnancy/lactation period have been provided by the Applicant. Therefore currently no conclusions can be drawn with regard to special risks in such populations.

- Safety related to drug-drug interactions and other interactions

No comprehensive information or formal analyses on possible drug-drug-interactions have been provided by the Applicant.
Many patients in the clinical trials had concomitant diseases and received appropriate medications. Most frequent were diseases of the cardiovascular system (about 40%), followed by disorders of the endocrine, the lymphatic and the musculoskeletal system.

- Discontinuation due to adverse events

Restless legs syndrome /TDS

In TULIR 01/01 no withdrawal occurred due to AEs. Application site reactions led to premature discontinuation in 18.8 to 32% in TULIR 02/01 in the lisuride groups, associated with a significant tendency towards an increased drop-out rate with increasing dose. Most adverse events leading to premature discontinuation in the lisuride group were rated as drug-related. Most prominent was the high number of discontinuations due to application site reactions (13.2%) followed by nausea (2%). There was an increased rate of dropouts due to skin and subcutaneous tissue disorders with increasing dose in TULIR 02/01: 4 (7.5%), 10 (18.9%), 13 (24.1%) and 16 (32.0%) patients in the placebo, 2.5 mg (10 cm^2), 5.0 mg (20 cm^2) and 10.0 mg (40 cm^2) lisuride groups, respectively. Altogether 25% of patients in the lisuride groups withdrew only due to drug related irritant skin reactions (dose dependently 19%-32%). No such dose relation was observed for other AEs that led to premature discontinuation of patients from the study. During the open label phase of study TULIR 02/01, 5.5% of patients discontinued prematurely due to ongoing application site (AS) reactions, 18.8% due to new AS reactions and further 1.7% due to other drug related skin reactions. Altogether 26% of patients in the OL period discontinued due to drug related skin reactions.

In TULIR 03/01, application site reactions led to premature discontinuations in 13.2% of patients.
In the open-label period of Study TULIR 03/01, newly occurred application site reactions led to discontinuation in 26% of patients. Ongoing application site reactions from DB period led to premature discontinuation of 3.5% of patients. Further 3.1 % of patients discontinued due to other drug-related newly occurred skin reactions. Again the discontinuation rate increased markedly with increasing dose of lisuride. Altogether at least 32.6% of patients in the OL period discontinued due to application site reactions and other drug related skin reactions.

Parkinson's disease/TDS

In the lisuride TDS group of TULIP IIb 20/168 patients had one or more treatment-related application site AEs that led to discontinuation: 13 with application site erythema, 2 with application site erythema and edema, 2 with application site reaction, 1 with application site reaction and irritation, 2 with application site dermatitis and 1 with application site eczema. In the placebo group, 2/165 patients experienced a treatment-related application site AE: application site reaction and application site erythema.

A treatment-related systemic AE that led to discontinuation was reported for 6/168 patients in the lisuride TDS group: 4 patients with hallucination, 1 with visual hallucination and 1 with orthostatic hypotension.

- Post marketing experience

There is no post marketing experience with lisuride transdermal patch.

- **Discussion on clinical safety**

A major concern with the Nenad transdermal system is the very high incidence of local skin reactions in the trials for the RLS indication (depending on the trial and period between at least 45% up to 80%

of the lisuride patients). Once affected, patients often experienced long persisting and/or over and over again, new occurring application site reactions. Despite these high numbers reporting was not sufficiently qualified to assess the true extent and duration of these reactions.

This in fact led to a high number of discontinuations due to drug-related local skin reactions, particularly in the DB period of TULIR 02/01 and in both OL (lisuride-only) periods till week 48 (25%, 26% and 33% patients respectively). Altogether around 50% of lisuride patients withdrew due to drug related local skin reactions in both RLS trials till week 48. Additionally, a considerable number of patients experienced strong/very strong and severe application site reactions respectively (depending of trial or trial period: between 14.1% in both RLS OL periods to 22.3% in DB period of TULIR 02/01).

In all trials and all periods of the Nenad TDS RLS trials (till week 48) there was a clear relationship between increasing dose and number as well as severity of local side effects. Moreover, in all trials and all periods (till week 48) there was an increase in the number of reported local side reactions with study duration. Additionally, in all periods of the RLS trials a not negligible number of patients used corticosteroids and antipruritic medications in order to treat adverse skin reactions. Presumably the number and/or severity of application site reactions would have been even higher without these concomitant medications.

Ergotamine-derived products like pergolide and carbergoline have been associated with the occurrence of irreversible pulmonary fibrosis and fibrosis of the cardiac valves. Lisuride is also an ergotamine derived dopamine agonists. However, in-vitro, lisuride lacks 5-HT_{2B} agonist activity, unlike pergolide. For the oral form that has been marketed since the 1980's, there were no reports of fibrosis of the cardiac valves, but several other fibrotic events did occur. However, as the expected incidence rate is low and exposure to oral lisuride has been limited thus far, an increased risk can not entirely be excluded.

No comprehensive information or formal analyses on possible drug-drug-interactions have been provided by the Applicant. Based on theoretical grounds, interactions with alcohol (sedative effects), dopamine antagonists like antipsychotics (antagonistic effects), and antihypertensive medicinal products (increased orthostatic hypotension) is expected.

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. The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substance has been adequately described. Most excipients used in this transdermal patch are well known excipients with the exception of the UV absorber, which has never been used via the cutaneous route. Full characterisation was deemed necessary but not provided. The manufacturing process was considered non-standard since the finished product is a modified release dosage form. Results from one production scale batch complemented by three clinical batches confirmed the robustness of the process. The shelf-life has not been fully establish since appropriate stability data

with the required updated specification regarding the parameters dissolution testing and adhesive properties have not been provided.

Non-clinical pharmacology and toxicology

Lisuride is a dopamine agonist with affinities for all known dopamine receptors, for 5-HT and for noradrenergic receptor subtypes. It has strong agonist effects at D2 and D3 receptors but also strongly binds to D4, D5 and D1 receptors; regarding the last one it can be considered to be a partial agonist.

The acute toxicity of lisuride is low. In repeated dose toxicity studies, the major effects were interpreted as an expression of increased dopaminergic activity.

Several genotoxicity studies have been performed. Despite of weak positive results in the Ames test in two Salmonella strains (TA1538, TQ 98), lisuride did not raise any further concerns as risk factors for mutagenic or carcinogenic effects *in vivo*. There were no indications for a carcinogenic potential of lisuride.

The potential effects of lisuride on reproduction have been evaluated in rats (fertility and early embryonic development, pre- and postnatal development) and in rats and rabbits (teratology). These studies do not indicate any teratogenic effects, but lisuride disturbed female fertility in that it dose-dependently decreased the pregnancy rates. Moreover, the embryo-mortality in rats was increased due the pharmacological, i.e prolactin-lowering, actions of lisuride. The potential risk for humans is unknown.

At the request of the CHMP, the applicant submitted during the assessment procedure two studies on local tolerance in rabbits and guinea pigs after prolonged and repeated administration of lisuride patches. Lisuride 10 cm^2 or placebo patches were applied on abraded as well as on non-abraded skin every 48 hours for 4 weeks. The study in rabbits demonstrated that, by comparing the test item to placebo, the incidence and severity of the reactions were slightly less in the placebo group. In guinea pigs the dermal application of the lisuride patch appeared to be well tolerated under the experimental conditions of the study.

During the assessment procedure, the applicant submitted *in vivo* data on phototoxicity in guinea pigs which show that lisuride or putative degradation products thereof cause skin irritation and that UVA irradiation (at 10J/cm^2 for 45 minutes exposure) potentiates this effect (from grade 1 to grade 2).

The lisuride patch includes an overtape containing a UV protective agent, which is in direct and indirect contact with the skin. In view of the applicants provided data, no toxic effects are expected for the UV absorber, if used as an excipient in the transdermal patch. However, the applicant has not provided the original studies on the irritation/sensitization and the genotoxicity of the UV absorber. This issue was not resolved during the assessment procedure.

Lisuride alters the concentration of the natural hormone prolactin and fulfils therefore the criteria of a potential endocrine disruptor. A risk assessment according to EMEA Guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00) is therefore required. This issue was not resolved during the assessment procedure.

Efficacy

For the indication Restless Legs Syndrome (RLS), the efficacy and safety of lisuride TDS has been investigated in one dose finding trial, TULIR 02/01, and one pivotal phase III trial, TULIR 03/01. The double-blind period of study TULIR 02/01 showed that the differences between all three Lisuride TDS dose groups (2.5mg, 5.0mg, 10mg) and placebo on the IRLS scale were statistically significant in favour of lisuride after 12 weeks treatment. Additionally, the 5mg and 10mg dose groups reached a difference vs. placebo on the IRLS scale at endpoint which was considered clinically relevant (a difference of -8.2 and -8.8 points, respectively). In the double blind period of study TULIR 03/01, the difference in the IRLS sum score after 12 weeks was statistically significant in favour of individually

optimized lisuride TDS over placebo (difference of -7.5 in the IRLS sum score, upper confidence limit -4.7). However, in the double-blind period of study TULIR 03/01 Lisuride TDS (dose range 2.5mg-7.5mg) missed the planned statistically significant superiority over the active comparator ropinirole (one-sided p-value 0.0381, point estimate -2.6, upper confidence limit 0.3). Additionally, it has to be considered that ropinirole was only permitted to be titrated up to 3mg and not up to 4mg, as permitted by the SmPC of ropinirole. The Applicant justified this decision with the average dose of 2mg ropinirole/d in the according pivotal trials. Nevertheless, this decision was critical, since 33.8% of the ropinirole patients were at the highest permitted dose level (3mg) at end of treatment.

Predefined responder- and remitter analyses of the double-blind periods of both trials supported the primary analyses. Most of the secondary parameters were in line with these results (with the exception of the 2.5 mg dose where the results were less favourable). In summary, the submitted data support short-term efficacy of Lisuride TDS 5 mg and 10 mg in the treatment of moderate to severe idiopathic RLS in adults.

Since RLS is a chronic, even life-long disease, robust long-term efficacy data are essential. These data are lacking. Data from open label extension trials were uncontrolled and hence there is not sufficient evidence for maintenance of efficacy. In addition, due to the very high discontinuation rates only 33% of the subjects remained in the trials.

The discontinuation rates of 37% in the lisuride groups of the double-blind period and of 47.7% in the open label (lisuride only) period of TULIR 02/01 as well as 35.5% in the lisuride group of the double-blind period and of 46.6% in the open label (lisuride only) period of TULIR 03/01 (till week 48) were very high. Approximately 2/3 of included patients of both trials discontinued prematurely between baseline of the double blind periods and week 48. When looking only at patients randomized to lisuride treatment already at double-blind baseline of TULIR 03/01 this number remains the same: only 33% of lisuride patients completed the core double-blind period and the open label period up to week 48. That is if continuation rate would be an indicator of treatment success, success would be only about 33%, which is not appropriate for a disease requiring chronic (even lifelong) symptomatic treatment.

A further major issue was the frequently inadequate patch adhesiveness. It is to be expected that efficacy of Lisuride TDS will be reduced frequently due to this issue, since a post-hoc subgroup analysis of the OL period of TULIR 03/01 has shown that patients with poor/moderate adhesiveness had markedly higher IRLS sum scores (as change from DB baseline) than patients with good/excellent adhesiveness.

Safety

The systemic drug-related adverse events in the RLS trials were those expected for a dopamine agonist and included headache, nausea, vomiting, dizziness, fatigue, vertigo and orthostatic hypotension. Systemic side effects occurred less frequently in the lisuride TDS group of the double-blind period of TULIR 03/01 than in the group of the active comparator ropinirole. Especially nausea was reported less often over the course of treatment with lisuride TDS (19.7%) than with ropinirole (35.9%).

The most important safety concern with lisuride TDS was the local skin reactions at the application site (depending of the trial and period between at least 45% up to 72% of the lisuride patients). The rate of adverse skin reactions in the double-blind periods of the RLS trials in patients treated with lisuride TDS were much higher than in patients treated with placebo patches, indicating that the local tolerance issues occurred mainly due to the active pharmaceutical ingredient lisuride. Furthermore, once affected patients often experienced long persisting, and/or over and over again, new occurring application site reactions. A considerable number of patients experienced strong/very strong and severe application site reactions respectively (depending on trial or trial period: between 10.5% in DB period of TULIR 03/01, 14.1% in both RLS OL periods up to 22.3% in DB period of TULIR 02/01). In all periods of the RLS trials a not negligible number of patients used corticosteroids and antipruritic medications in order to treat adverse skin reactions. Presumably the number and/or severity of application site reactions would have been even higher without these concomitant medications.

Furthermore, application of local corticosteroids has their own risk of local side reactions, such as skin atrophy, particularly if given over a longer time-period. A transdermal treatment of RLS requiring repeated or long-term application of corticosteroid-containing ointments in many patients is hardly justifiable. Further, the high incidence of local application reactions will also affect efficacy, either directly (change of absorption through the inflamed skin) or indirectly (loss of adhesiveness).

Risk-benefit assessment

Individually optimized lisuride TDS has shown short-term efficacy for 12 weeks regarding symptomatic treatment of moderate to severe idiopathic RLS in adults. However, no valid final conclusion on long-term efficacy can be drawn due to the lack of controlled long term efficacy trials and the high drop out rates both in the double-blind and the open label periods.

The very high discontinuation rates in the double-blind periods of the RLS trials and the according open label periods till week 48 are a major concern. Only 33% of lisuride patients in the pivotal study TULIR 03/01 completed the core double-blind period and the open label period up to week 48, which is not considered appropriate for a disease requiring chronic symptomatic treatment.

Very high rates of drug related irritant skin reactions were observed in the RLS trials. Frequency of skin reactions increased with study duration and there was a clear relationship between increasing dose and number as well as severity of local side effects. A major issue was also the very frequently occurring inadequate patch adhesiveness which had negative consequences with respect to efficacy and handling of the patch.

Due to the aforementioned concerns, the risk-benefit balance of lisuride TDS in the treatment of idiopathic RLS is negative. At the Oral Explanation the Applicant discussed the aforementioned concerns, but the CHMP considered that the risk-benefit balance of lisuride TDS in the treatment of Restless Legs Syndrome remained negative.

Conclusions

In conclusion, the CHMP considers that, following review of the data provided, there are major concerns with respect to the risk-benefit of Nenad in the treatment of Restless Legs Syndrome on the following grounds:

- Long-term efficacy of lisuride transdermal patch for the treatment of Restless Legs Syndrome has not been established. The high rate of premature discontinuations in the trials and the open label uncontrolled data do not allow demonstration of maintenance of efficacy.

- The very high rate of premature discontinuations in the clinical studies due to drug-related irritant skin reactions indicates that lisuride transdermal patch as it was studied in the present application is not suitable for use in clinical practice.

- The high rate of inadequate adhesiveness of the transdermal patch had negative consequences for the efficacy and handling of the patch.

- Due to the aforementioned concerns, a satisfactory summary of product characteristics, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Nenad in the treatment of Restless Legs Syndrome was unfavourable and therefore did not recommend the granting of the marketing authorisation.