Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rotigotine

Proprietary Product Name: Neupro

Sponsor: UCB Australia Pty Ltd

January 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications Registration of Two New Strengths
Decision:	Approved
Date of Decision:	8 October 2010
Active ingredient(s):	Rotigotine
Product Name(s):	Neupro
Sponsor's Name and Address:	UCB Australia Pty Ltd Level 1, 1155 Malvern Road Malvern Vic 3144
Dose form(s):	Transdermal patch
Strength(s):	1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h
Container(s):	Sachet containing one patch
Pack size(s):	Each strength is available in a pack of 7, 28 or 100 sachets
Approved Therapeutic use:	Parkinson's disease Neupro is indicated as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease. Restless Legs Syndrome Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.
Route(s) of administration:	Transdermal
Dosage:	Dosage is dependent on the indication and for Parkinson's disease, the stage of the disease. For the newly approved indication, Restless Legs Syndrome, a single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h.
ARTG Number (s)	131370, 131381, 131382, 131383, 163987, 163988

Product Background

Neupro (rotigotine) is currently indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or in combination with levodopa, over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or 'on-off' fluctuations). In the current submission, the sponsor proposes to expand the indication of rotigotine to include the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS).

Restless Legs Syndrome can be described as a neurological sensorimotor disorder with irresistible leg movements that are often accompanied by creeping sensations deep in the limbs. The symptoms of RLS are not confined to the legs, but can also occur in the upper limbs. The majority of symptoms of RLS occur in the evening and at night. Lying down in bed is associated with increased paraesthesia and an irresistible urge to move, often accompanied by periodic limb movements which interfere with sleep onset and with consolidation of sleep.

Restless Legs Syndrome is one of the most frequent neurological diseases, with an estimated prevalence of 7% to 11% of the general population.[1]

In recent years, the International Restless Legs Syndrome Study Group (IRLSSG) has developed and validated the International Restless Legs Syndrome Study Group Rating Scale (IRLS), a subject-based rating scale that assesses the severity of RLS (Walters et al, 2003).[2] The IRLS has been used in clinical trials with dopamine agonists (for example, cabergoline, pergolide, ropinirole, and pramipexole) and represents an increasingly accepted international standard for the clinical assessment of RLS severity (Trenkwalder et al, 2004; Freeman et al, 2001, Winkelman et al, 2006).[3,4,5] This scale is used as an inclusion criterion to assess the severity of disease and as one of the main outcome measures in the clinical trials presented. The Clinical Global Impression (CGI) rating scales are physician-rated measures of symptom severity, treatment response, efficacy, and side effects (Table 1). CGI-Item 1 Severity of Illness score, together with the IRLS sum score, were the primary efficacy outcome measures in the two pivotal phase III efficacy studies.

Table 1: Clinical Global Impression Rating Scale

Item 1, Severity of Illness	7 point scale: 0=not assessed, 1=normal, not ill at all, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill
Item 2, Global Rating of Change of Condition	7 point scale: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse
Item 3, Therapeutic Efficacy	4 point scale: 0=not assessable, 1=very good, 2=moderate, 3=slight, 4=unchanged or worse
Item 4, Side effects	4 point scale: 0=not assessable, 1=none, 2=they do not significantly interfere with subject's functioning, 3=they

[1] EMA. Assessment report for Neupro; Procedure No. EMEA/H/C/626/II/0019. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000626/WC500026743.pdf: accessed 12 August 2010

[2] Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al; the International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003; 4: 121-32.

[3] Trenkwalder C, Garcia-Borreguero D, Montagna P et al. Ropinerole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomized, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004; 75: 92-7.

[4] Freeman A, Rye DB, Bliwise D, Chakravorty S, Krulewicz S, Watts RL. Ropinirole for Restless Legs Syndrome (RLS): An open-label and double-blind placebo-controlled study. Neurology 2001; 56: S02.005.

[5] Winkelman JW, Sethi KD, Kushida CA et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006; 67: 1034-9.

	significantly interfere with subject's functioning, 4=they outweigh therapeutic efficacy.

As disrupted sleep is a major complaint for patients with RLS, it is thought that objective sleep data may help characterise the therapeutic efficacy of dopamine agonists (Allen et al, 2004).[6] Sleep laboratory studies can provide objective data on periodic limb movements (PLMs) during the night, sleep stages, arousals and awakenings. The sponsors have conducted one sleep study involving 46 patients (SP794).

To date, there are no methods of chronic, continuous drug delivery of dopamine agonists for RLS patients. Rotigotine is a non-ergolinic dopamine agonist with a high *in vitro* affinity for all dopamine receptor subtypes. Affinity is particularly high for the D3 receptor, about 10-fold less for the D2 and about 100-fold less for the D1 receptor. It also has high intrinsic (agonistic) activity on all dopamine receptor subtypes which, again, is particularly high for the D3 subtype. It has been developed to provide continuous drug delivery with once-daily dosing via a transdermal patch.

In Australia, Neupro (rotigotine) transdermal patch is currently available in the following strengths: 2 mg/24 hour, 4 mg/24 hour, 6 mg/24 hour and 8 mg/24 hour (h).

The proposed dosage regimen for treatment of RLS is a single daily dose initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximum dose of 3 mg/24 h. This requires the registration of two new strengths: 1 mg/24 h and 3 mg/24 h.

The current approved indication in Australia is:

Neupro is indicated as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease.

The purpose of this Application is to extend the indication to include the treatment of RLS. The proposed indication is:

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

Regulatory Status

Neupro was approved via the European Centralised Procedure for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease on 15 Feb 2006. Subsequently, the indication was extended to include treatment of advanced stage Parkinson's disease. The currently authorised indication is:

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or 'on-off' fluctuations).

The European Union (EU) approved the extension of indication to RLS on 29 August 2008 in the same three strengths which have been requested in the current Australian submission. The approved indication is:

[6] Allen R, Becker PM, Bogan R et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep. 2004; 27: 907-14.

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults

The same indication has also been approved in Switzerland.

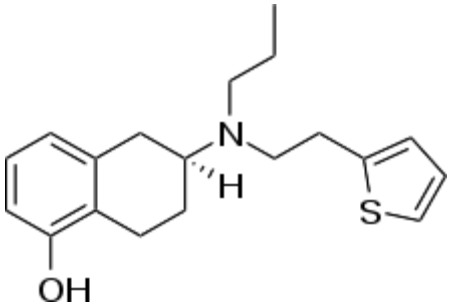
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Rotigotine has the chemical formula (6S)-6-{propyl-[2-(2- thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol with a structure as shown.



Molecular Formula: $C_{19}H_{25}NOS$

Molecular Mass: 315.48 g/mol

CAS No: **99755-59-6**

Drug Product

Formulation

Due to the low bioavailability of oral rotigotine, rotigotine has been developed for transdermal administration using patch technology. This design allows continuous drug delivery, improves the bioavailability and may provide a more stable plasma concentration compared to orally administered drugs. The patches are manufactured by Lohmann Therapie Systeme Andernach (Germany) for Schwarz Pharma. The commercial formulation is a silicone-based matrix patch and this formulation was used in most of the clinical trials.

For this indication, 3 strengths of rotigotine transdermal patch containing 2.25, 4.5, or 6.75 mg are proposed. The patches provide nominal doses of 1, 2, or 3 mg of rotigotine per 24 hours respectively, delivered to the skin. Doses were converted using the following formula: dose in mg/24 h=dose in mg/day divided by 2.25. The quantitative composition per area is identical for all strengths, and the nominal delivery per cm^2 is 0.2 mg/24 hours. The different strengths correspond to patch sizes of 5, 10, and 15 cm^2, respectively.

Specifications

The finished product release and expiry specifications have been amended as requested, by updating the test method for content uniformity from the European Pharmacopoeia (Ph. Eur.) 2.9.6. to Ph. Eur. 2.9.40. In addition, the limit for N-propyl-N-(2thienylethyl) hydroxylamine at release has been tightened. These amendments have also been made to the registered 2 mg/24 h patch, which is also proposed for the treatment of restless legs syndrome. The revised release and expiry specifications are now considered satisfactory.

Stability

Stability data were provided for the four batches of each strength patch, including the registered strengths (24 batches in total) that had been manufactured using the process from polymorphic Form 2 (see page 12). Most results were satisfactory and were consistent with previously reported results. After storage for 12 months at 5°C, the amount of crystallisation was less than 1% in all batches but one. The extent of the crystallisation in that batch was 3%, well within the limit of 10%. At 25°C, the extent of crystallisation was greater, but only exceeded 10% in one batch after 3 months, where it reached 38%. This batch reached 70% crystallisation after 6 months at 25°C. All batches exceeded the 10% crystallisation after 6 months at 25°C. Most batches complied with the dissolution specification under all conditions except for one which had a low dissolution rate after 6 months at 25°C.

Given that only one of the 24 batches exceeded the crystallisation limit after 3 months' storage at 25°C, and given that all batches had very low amounts of crystallisation after 12 months storage at 5°C, extrapolation of the shelf life to 24 months at 2-8°C, as already approved for the registered strengths, is considered warranted.

Quality Summary and Conclusions

There were no objections in respect of chemistry, manufacturing and controls to registration of the additional strengths of Neupro transdermal patches.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The studies in the submission included:

- 3 comparative bioavailability and bioequivalence studies (SP871, SP651, and SP951);
- 3 pharmacokinetic (PK) studies including one population PK study (SP861, SP 862, SP790-SP792)
- 1 pharmacodynamic (PD) study (a Thorough QT/QTc trial, SP864);
- 5 controlled clinical studies in restless legs syndrome, including 2 pivotal Phase III trials (SP790 and SP792), a Phase IIa study (SP666), a Phase IIb study (SP709), and a sleep laboratory study (SP794);
- 3 open label clinical studies (SP710, SP791 and SP793).

The efficacy trials are summarised in Table 2.

Table 2: Trials evaluation efficacy of rotigotine patch in RLS

Protocol number	Trial design	Rotigotine dose	Treatment duration	Total number of unique subject exposures to rotigotine (SS)
Primary efficacy trials				
SP790	Multicenter, DB, PC, fixed-dose	1, 2, or 3mg/24h	Approximately 7 months	341[a]
SP792	Multicenter, DB, PC, fixed-dose	0.5, 1, 2, or 3mg/24h	Approximately 7 months	404
Long-term trials				
SP710	Multicenter, OL	0.5, 1, 2, 3, or 4mg/24h	Up to 5 years	295 (46 new exposures)[b]
SP791	Multicenter, OL	1, 2, or 3mg/24h	Up to 1 year	341 (76 new exposures)[b]
SP793	Multicenter, OL	0.5, 1, 2, or 3mg/24h	Up to 1 year	278 (59 new exposures)[b]
Supporting trials				
SP666	Multicenter, DB, PC, fixed-dose	0.5, 1, or 2mg/24h	7±1 day	49
SP709	Multicenter, DB, PC, fixed-dose	0.5, 1, 2, 3, or 4mg/24h	7 weeks	285
SP794	Multicenter, DB, PC, dose-escalation to optimal dose	1, 2, or 3mg/24h	Up to 8 weeks	46

DB=double-blind; OL=open-label; PC=placebo-controlled; RLS=Restless Legs Syndrome; SS=Safety Set

a Total rotigotine exposure was 344 subjects because 3 subjects randomized to placebo were treated in error with rotigotine

b New exposures include subjects who received placebo in the preceding double-blind trial

The submission also included reports for bioanalytical and analytical methods for the human studies, integrated analyses of efficacy and safety and post-marketing experience reports, including two Periodic Safety Update Reports (PSURs).

The sponsor certified that all clinical studies were carried out in accordance with the Declaration of Helsinki and International Conference of Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

Pharmacodynamics

Mode of Action

Rotigotine is a non-ergolinic dopamine agonist with a high *in-vitro* affinity for D3/D2/D1 dopamine receptor subtypes and low oral bioavailability. A single pharmacodynamic study assessed the electrocardiographic effects of supra-therapeutic doses of transdermal rotigotine in 130 subjects with advanced-stage idiopathic Parkinson's disease.

Electrocardiographic effects

A double-blind, randomised, placebo- and positive-controlled, parallel-group trial (**SP864**) was conducted to assess the potential electrocardiographic effects of the rotigotine transdermal system at doses up to 120 cm^2/54.0 mg/day in 130 subjects (41 female), aged 29 to 88 years, with advanced-stage idiopathic Parkinson's disease.

Subjects were assigned to receive treatment with either a rotigotine patch, at doses from 9.0 mg/day to 54.0 mg/day (66 subjects) or a placebo patch (64 subjects). Placebo subjects were randomised to receive either placebo saline intravenous (IV) solution or moxifloxacin IV

solution (positive control) on Days 32 and 39 in a crossover design, while all subjects in the rotigotine group received placebo saline IV on both days.

The treatment phase consisted of a 42 day dose escalation phase during which subjects received ascending doses of rotigotine (9 mg/day to 54 mg/day doses; incremental increases of 9 mg every 7 days). This was followed by a 10 day de-escalation phase (45/36/27/18/9 mg decreasing doses, every 2 days). A total of 130 subjects were randomised and treated with trial medication and therefore analysed for safety. Ninety-one subjects were analysed for the primary pharmacodynamic variable and 31 subjects were analysed for assay sensitivity. All 130 randomised subjects were analysed for pharmacokinetic variables.

Results for the primary pharmacodynamic variable, the time-matched change from baseline in the QT interval corrected for heart-rate according to individual correction factor (QTcI) over 4-hour intervals during the daytime on Day 43 (54.0 mg/day rotigotine), showed that supratherapeutic doses of rotigotine did not prolong the QT interval. The point estimates for the mean difference for the parallel group comparison of the time-matched change from baseline between rotigotine (54.0 mg/day) and placebo in 4-hour area under the concentration-time curve (nAUC)(QTcI) on Day 43 ranged from -1.25 to -0.33 milliseconds (ms). For all 4-hour time intervals, the 2-sided upper limits of the 90% confidence intervals (CI) were below the 10 ms non inferiority margin (range: 0.59 to 1.55). No subjects in either treatment group had AUC(QTcI) values of ≥480 ms or a change from baseline of ≥30 ms at any of the time intervals.

Assay sensitivity was assessed by examining the effects of moxifloxacin versus placebo on the change in nAUC(QTcI) over a 1-hour time interval. For the primary variable, the mean difference between moxifloxacin and placebo was 11.30 ms and the lower 95% confidence limit was 9.31 ms, indicating a statistically significant effect of moxifloxacin compared to placebo.

Analysis of the change from baseline for the 4-hour nAUC(QTcI) at 18, 27, 36 and 45 mg/day rotigotine also showed no prolongation of QTcI.

Pharmacokinetics

The pharmacokinetics of rotigotine were examined in four trials comprising 202 healthy subjects and a further 2 trials in 166 subjects with idiopathic Parkinson's disease (PD). A single study comprising the results from 2 clinical trials (SP790 and SP792) examined the population pharmacokinetics of rotigotine in 962 subjects with restless legs syndrome (RLS).

No new data regarding the absorption/distribution/metabolism/excretion (ADME) profile of the rotigotine transdermal patches to be used for RLS were provided in this submission. However, the ADME profile of the rotigotine transdermal patches has already been studied and the evaluators briefly summarised the ADME profile from the approved rotigotine PI (for treatment of PD):

Following transdermal application, rotigotine is continuously released from the patch and absorbed through the skin. Steady state concentrations are reached after one to two days of patch application and are maintained at a stable level by once daily application in which the patch is worn for 24 hours. Rotigotine plasma concentration increases dose proportionally over a dose range of 1 mg/24 hours to 24 mg/24 hours. Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal patch application is approximately 37%.The *in vitro* binding of rotigotine to plasma proteins is approximately 92%. The apparent volume of distribution in humans is approximately 92%. Rotigotine is extensively metabolised by N-dealkylation as well as direct or secondary conjugation. *In vitro* studies suggest that different cytochrome P450 (CYP)

isoforms are able to catalyse the N-dealkylation of rotigotine. Although the information on metabolites is incomplete the main metabolites are thought to be sulphates and glucuronide conjugates of the parent compound as well as N-dealkyl-metabolites. Approximately 71% of the rotigotine dose is excreted in urine and a small part, about 23%, is excreted in faeces. The clearance of rotigotine following transdermal administration is approximately 10 L/min and its elimination half-life is 5 to 7 hours.

Comparative bioavailability / bioequivalence studies

Study SP871

A single-site, randomised, open-label, crossover trial (**SP871**) assessed the relative bioavailability of rotigotine, at steady state, following administration of a single rotigotine transdermal patch 6.75 mg/15 cm^2 compared to combined application of 1 x 2.25 mg/5 cm^2 plus 1 x 4.5 mg/10 cm^2 rotigotine patches in 56 healthy male subjects, aged 18 to 45 years.

After a 3-day run-in period with once daily application of one 4.5 mg (10 cm^2) rotigotine transdermal patch, rotigotine patches (6.75 mg [15 cm^2]/day) were applied in a randomised sequence of 6 different application sites on Days 4 to 12. On Days 13 and 14, patches were applied to the same application site as on Day 12 in a crossover design in which subjects received Treatment A (one 6.75 mg [15 cm^2] patch) and Treatment B (one 2.25 mg [5 cm^2] plus one 4.5 mg [10 cm^2] patch) in randomised order. A secondary objective of this trial was to evaluate the relative bioavailability of rotigotine after patch application (6.75 mg [15 cm^2]) to 6 different application sites (shoulder, upper arm, flank, abdomen, hip and thigh).

All subjects received at least 1 dose of trial medication and were therefore included in the Safety Set (SS). Forty-one subjects completed the trial according to the protocol. Complete pharmacokinetic data was available for 40 subjects who formed the Pharmacokinetic Set (PKS).

The mean plasma concentrations and primary PK parameters after application of one 6.75 mg (15 cm^2) rotigotine patch (Treatment A) versus concomitant application of one 4.5 mg (10 cm^2) plus one 2.25 mg (5 cm^2) rotigotine patch were similar (Table 3).

Table 3: PK parameters of unconjugated rotigotine by treatment (Days 13-14) (PKS in SP871)

Parameter	Geo mean (geo CV[%])[a]	
	A (n=40)	B (n=40)
$AUC_{(0-24),ss}$ (ng/mL*h)	9.1194 (45.6)	9.5627 (45.5)
$AUC_{(0-24),ss,norm}$ (ng/mL*h/mg)	2.6658 (40.8)	2.8551 (32.0)
$C_{max,ss}$ (ng/mL)	0.52247 (45.3)	0.53711 (43.5)
$C_{max,ss,norm}$ (ng/mL/mg)	0.15273 (40.8)	0.16036 (33.0)
$t_{max,ss}$ (h)[a]	16.0 (0-24)[a]	16.0 (2-20)[a]

A=one 6.75mg (15cm^2) rotigotine patch, B=one 4.5mg (10cm^2) + one 2.25mg (5cm^2) rotigotine patch, CV=coefficient of variation, geo=geometric, n=number of subjects assessed, PKS=Pharmacokinetic Set

The ratios of the geometric means were 95% for $AUC_{(0-24),ss}$ and 97% for $C_{max,ss}$. The respective 90% CIs for $AUC_{(0-24),ss}$ and $C_{max,ss}$ were (91%, 100%) and (92%, 103%), respectively, which were both within the acceptance range for bioequivalence of 80% to 125%. Thus, the bioavailability following one 6.75 mg (15cm^2) patch was similar to that following combination of one 4.5 mg (10cm^2) plus one 2.25 mg (5cm^2) patch.

Application of one 6.75 mg (15 cm^2) rotigotine patch to 6 different application sites resulted in values for $AUC_{(0-24),ss}$ ranging from 7.7 ng/mL.h (coefficient of variation [CV]:41.2%) (thigh) to 10.8 ng/mL.h (CV: 32.5%) (flank) with slightly lower AUC values for the abdomen, hip and thigh compared to the shoulder, upper arm and flank.

Following dose normalisation, pairwise comparisons of the area under the concentration-time curve during a dosing interval at steady state normalized by apparent dose ($AUC_{(0-24),ss,norm}$) of unconjugated rotigotine for different application sites resulted in point estimates ranging from 91.8% to 111.0% and the 90% CIs for all pairwise comparisons of $AUC_{(0-24),ss,norm}$ were within the range of bioequivalence.

Following normalisation of apparent dose, pairwise comparisons of the maximum observed plasma or serum concentration during a dosing interval at steady state normalized by apparent dose ($C_{max,ss,norm}$) of unconjugated rotigotine for different application sites resulted in point estimates ranging from 86.9% to 114.1%. The 90% CIs were within a range of 80% to 125% for 14 of the 15 pairwise comparisons and within the range of 70% to 143% for the comparison flank versus hip (79.7, 94.9).

Study SP651

A single-centre, randomised, open-label crossover trial (**SP651**) assessed the relative bioavailability of rotigotine after multiple-dose applications of rotigotine transdermal patch (18.0 mg/40 cm^2 or 2 x 9.0 mg/20 cm^2) at different sites of application in 36 subjects (14 female), aged 46 to 85 years, with idiopathic PD. Rotigotine patches (18.0 mg [40 cm^2]/day) were applied to a randomised sequence of 6 different application sites. At the sixth site, patches were applied in a cross-over design in which subjects received treatment A (one 18.0 mg [40 cm^2] rotigotine patch) and treatment B (two 9.0 mg [20 cm^2] rotigotine patches) in randomised order.

Following administration of Treatment A (one 18.0 mg [40cm^2] patch), mean steady state rotigotine plasma concentrations from the previous patch applied on Days 20 and 21 decreased from 0.80 ± 0.41 ng/mL to 0.57 ± 0.27 ng/mL within 2 hours followed by an increase to plateau plasma concentrations. The highest mean plasma concentration of rotigotine was reached 20 hours after patch application (1.11 ± 0.58 ng/mL). Immediately prior to patch removal, the mean plasma concentration of rotigotine was 0.80 ± 0.42 ng/mL.

Following administration of Treatment B (two 9.0 mg[20 cm^2] patches) mean steady state rotigotine plasma concentrations decreased from 0.83 ± 0.43 ng/mL to 0.61 ± 0.31 ng/mL within 2 hours followed by an increase to plateau plasma concentrations. The highest mean plasma concentration of rotigotine was reached 20 hours after patch application (1.09 ± 0.54 ng/mL). Immediately prior to patch removal, the mean plasma concentration of rotigotine was 0.82 ± 0.45 ng/mL.

The geometric means for $AUC_{(0-24)ss}$, $C_{max,ss}$ and the median time to reach the observed maximum (peak) concentration at steady state ($t_{max,ss}$) were very similar for both treatments. In addition, the mean apparent doses and the PK parameters normalised by apparent dose parameters were similar for both treatments. The $AUC_{(0-24)ss}$ and $C_{max,\ ss}$ were bioequivalent for the two treatments.

When analysed for application site, similar mean $AUC_{(0-24)ss}$ and $C_{max,ss}$ values were obtained for upper arm, abdomen, flank, hip, and thigh, whereas application of patches to the shoulder resulted in higher mean $AUC_{(0-24)ss}$ and $C_{max,ss}$. The median $t_{max,ss}$ for shoulder was 12.0 hours, whereas it was 16 hours for most of the other application sites. When normalised for apparent dose, the $AUC_{(0-24)ss,norm}$ and $C_{max,ss,norm}$ were slightly higher for shoulder compared to the other application sites.

The ratios of geometric means for pair wise comparisons between the various application sites suggest that the site of patch application can cause robust changes in both the $AUC_{(0-24)ss}$ and $C_{max,\ ss}$ of rotigotine. In particular, when applied to the shoulder, the ratio of the $AUC_{(0-24)ss}$ ranged from 130 - 164% and $C_{max,\ ss}$ 123 to 148% higher compared to the other application sites and the 90% confidence limits were outside the range of bioequivalence (80-125%). Although the difference between shoulder and the other application sites was reduced when the normalised apparent dose was examined, $AUC_{(0-24)ss}$, norm (111.26% – 133.98%) and $C_{max,ss}$, norm (105.03% – 119.62%), the normalised results indicate a higher absorption of rotigotine when the patch was applied to the shoulder.

Study SP951

After marketing authorisation, a new polymorphic form of the drug substance rotigotine was identified. The new polymorphic form (Form 2) differed in some of the physicochemical properties from those of the original polymorphic form (Form 1). Form 2 is thermodynamically more stable with a lower solubility in most of the solvents tested and with a higher melting point than Form 1. During drug substance synthesis, pure Form 2 is now manufactured and the process is validated. Consequently, the commercial patch manufacturing process has been changed using pure Form 2 for patch production.

Hence, a single-site, open-label, randomised, crossover trial (**SP951**) evaluated the bioequivalence of a single dose rotigotine transdermal patch (4.5 mg/10 cm^2) from the 2 different manufacturing processes. Fifty-two male subjects, aged 20 to 50 years, received in random order a single-dose application of rotigotine transdermal patch (4.5 mg/10cm^2) for 24 hours from a modified manufacturing process (Form 2) and a single dose of rotigotine transdermal patch (4.5 mg/10cm^2) for 24 hours from the originally approved manufacturing process (Form 1). Subjects received both treatments in a cross-over design separated by a wash-out period of at least 5 days. All fifty two subjects were included in the SS and 44 subjects were included in the PKS.

The mean plasma concentrations and primary PK parameters were very similar between the 4.5 mg/10cm^2 Form 2 rotigotine patch and the 4.5 mg/10cm^2 Form 1. The ratios of geometric means for $AUC_{(0-tz)}$ and C_{max} were 0.99 and 0.96, respectively and the 90% confidence intervals for both $AUC_{(0-tz)}$ (0.91,1.07) and C_{max} (0.89, 1.04) were contained within the accepted level of bioequivalence. The point estimates for the ratio of the PK parameters $AUC_{(0-tz)}$ and C_{max} corrected for drug content were 1.01 and 0.98 respectively and the 90% CIs were within the level of bioequivalence and thus support the uncorrected analysis. The mean absolute apparent doses were similar for Treatments A and B and the mean apparent doses relative to drug content were also similar between treatments (37.25% compared to 41.98%, respectively).

Therefore, the patches from the two manufacturing processes appear to be bioequivalent in regards to their AUC and C_{max}.

Extrinsic Factor PK

Drug Interactions with Oral Hormonal Contraception

A randomised, double-blind, placebo-controlled, crossover, multiple-dose trial (**SP861**) investigated the influence of 6.75 mg rotigotine on the suppression of ovulation by oral hormonal contraception in 40 healthy female subjects, aged 20 to 35 years. Following a 2-month run in period on oral hormonal contraception, subjects concomitantly received a rotigotine or placebo patch in a randomised crossover sequence for 2 treatment cycles. Each cycle lasted 28 days during which patch medication was administered on Days 1 through 13.

Mean serum concentrations of progesterone varied between 0.45 ng/mL and 0.46 ng/mL after treatment (A) with rotigotine, and between 0.46 ng/mL and 0.48 ng/mL after treatment (B) with placebo patch. The maximum progesterone serum concentration measured was 1.16 ng/mL after rotigotine treatment and 1.21 ng/mL after treatment with placebo patch. None of the subjects reached a serum concentration of progesterone of ≥2 ng/mL during Days 19 to 21 after either treatment, indicating sufficient suppression of ovulation, regardless of whether subjects were treated with rotigotine or placebo patch.

Median oestradiol serum concentrations ranged between 0.00 pg/mL and 14.50 pg/mL in subjects treated with rotigotine and between 0.00 pg/mL and 13.95 pg/mL in subjects treated with the placebo patch. The highest individual serum concentrations of oestradiol reached were 51.10 pg/mL in subjects treated with rotigotine and 32.30 pg/mL in subjects treated with the placebo patch, respectively. All of the oestradiol serum concentrations measured fell within the normal range of non-ovulatory female subjects.

Median luteinising hormone (LH) serum concentrations ranged between 1.0 U/L and 2.9 U/L in subjects treated with rotigotine and between 0.7 U/L and 2.0 U/L in subjects treated with the placebo patch. The highest individual serum concentrations of LH reached were 12.8 U/L in subjects treated with rotigotine and 8.6 U/L in subjects treated with placebo patch. All of the LH serum concentrations measured fell within the normal range of non-ovulatory female subjects. Median follicle stimulating hormone (FSH) serum concentrations ranged between 0.0 U/L and 1.8 U/L in subjects treated with rotigotine and between 0.0 U/L and 1.5 U/L in subjects treated with placebo patch. The highest individual serum concentrations of FSH reached were 5.1 U/L in subjects treated with rotigotine and 4.8 U/L in subjects treated with the placebo patch. All of the FSH serum concentrations measured fell within the normal range of non-ovulatory female subjects.

Oestradiol, LH, and FSH serum concentrations were sufficiently suppressed by the hormonal contraceptive at all time points measured, regardless of whether subjects were treated with rotigotine or placebo patch.

Mean plasma concentrations of ethinyloestradiol rose from trough values of 36.8 ± 112.0 pg/mL (rotigotine) and 21.7 ± 20.8 pg/mL (placebo patch) at 0 hours (pre-dose) to a maximum mean of 102.2 ±91.7 pg/mL (rotigotine) and 88.6 ± 25.3 pg/mL (placebo patch), respectively, at 1.5 hours after administration of oral hormonal contraceptive. After having reached maximum values, ethinyloestradiol plasma concentrations continually decreased to trough values of 29.4 ± 61.7 pg/mL (rotigotine) and 21.0 ± 12.7 pg/mL (placebo patch) by 24 hours. Both mean plasma concentrations versus time profiles of ethinyloestradiol exhibited a comparable pattern with or without rotigotine, with slightly higher mean plasma concentrations of ethinyloestradiol during concomitant treatment with rotigotine. Inter-individual variability of plasma concentrations was higher under rotigotine treatment than placebo patch as expressed by the higher standard deviation (SD) values. Median plasma concentrations were nearly identical under both treatments. The median values of $t_{max,ss}$ for

ethinyloestradiol were similar for both treatments, whereas the geometric means of $AUC_{(0-24),ss}$ and $C_{max,ss}$ were slightly higher following rotigotine treatment than placebo. Variability of both $AUC_{max,ss}$ and $C_{max,ss}$ was slightly higher following rotigotine administration. These findings can be explained by the effect of the (individual) PK values observed for one subject following rotigotine treatment. For this subject, values of 11658 pg/mL.h and 689.0 pg/mL were determined for $AUC_{max,ss}$ and $C_{max,ss}$ for ethinyloestradiol during rotigotine treatment. These values were approximately 12- and 7-fold higher respectively than those of all other subjects in the PKS. The point estimates (ratio A/B) for the comparison of rotigotine versus placebo treatment for both PK parameters $AUC(0-24)_{,ss}$ and $C_{max,ss}$ were both 1.05 and the 90% CIs for the ratio A/B were within the acceptance range for bioequivalence.

Mean plasma concentrations of levonorgestrel increased from trough values of 2544.6 ± 1137.2 pg/mL (rotigotine) and 2695.6 ± 1375.8 pg/mL (placebo) at 0 hours (pre-dose) to maximum mean values of 6796.7 ± 2482.9 pg/mL (rotigotine) and 6717.8 ± 2495.3 pg/mL (placebo patch) at 1 hour following administration of the oral contraceptive. After reaching maximum values, mean levonorgestrel plasma concentrations decreased to trough levels of 2690.9 ± 1239.8 pg/mL (rotigotine) and 2812.4 ± 1360.8 pg/mL 24 hours following administration of the contraceptive. Mean plasma concentrations versus time profiles of levonorgestrel exhibited a similar pattern in the presence and absence of concomitant administration of rotigotine. Moreover, inter-individual variability of plasma concentrations, as expressed by SD values, was comparable for both treatments. These results suggest that rotigotine has little impact on the plasma concentrations over time of levonorgestrel. Levonorgestrel plasma concentrations >limit of quantification (LOQ) (> 50 pg/mL) at Day 1 (pre-dose) were measured in 69.4% of subjects in the rotigotine treatment cycle and 63.9% of subjects in the placebo patch treatment cycle. Maximum plasma concentrations of levonorgestrel at Day 1 were 391 pg/mL (prior to rotigotine treatment) and 373 pg/mL (prior to treatment with placebo patch), respectively. These concentrations fall within the range expected from a drug with a half-life of 25 hours, such as levonorgestrel (Microgynon package insert) after incomplete washout between cycles.

The median values of $t_{max,ss}$ for levonorgestrel were 1 hour for both treatment groups and the ranges of $t_{max,ss}$ were comparable. Geometric means of $AUC_{(0-24),ss}$ (81799 and 83665 pg/mL.h, respectively) and their CV values were similar as were the geometric means of $C_{max,ss}$ (6763 and 6714 pg/mL, respectively) and their CV values. The point estimates (ratio A/B) for the comparison of rotigotine versus placebo treatment for both PK parameters $AUC_{(0-24),ss}$ and $C_{max,ss}$ were 0.98 and 1.01, respectively, and the 90% CIs for the ratios A/B were within the acceptance range for bioequivalence. Mean plasma concentrations of unconjugated rotigotine remained stable throughout the patch-on period on Day 13 and ranged from 0.4 ± 0.2 ng/mL to 0.6 ± 0.3 ng/mL. Mean plasma concentrations of total rotigotine also remained stable throughout the patch-on period on Day 13 and ranged from 1.6 ± 0.8 ng/mL to 1.8 ± 0.7 ng/mL. For unconjugated rotigotine, the mean maximum concentration at steady state ($C_{max,ss}$) was 0.6 ng/mL and occurred at a $t_{max,ss}$ of 16 hours. Normalisation by apparent dose resulted in an $AUC_{(0-24),ss,norm}$ of 3.0ng/mL.h/mg (CV%=34.8%) and $C_{max,ss,norm}$. of 0.16ng/mL/mg (CV%=31.6%). For total rotigotine, the $C_{max,ss}$ was 2.01 ng/mL and occurred at a $t_{max,ss}$ of 6 hours. Normalisation by apparent dose resulted in an $AUC_{(0-24),ss,norm}$ of 10.6ng/mL.h/mg (CV%=36.3%) and $C_{max,ss,norm}$. of 0.56ng/mL/mg (CV%=33.7%).

Depending on the application site, the apparent dose of rotigotine ranged from (mean±SD) 3.2 ± 0.6 mg (47.8 ± 9.3%), following application to the thigh, to 4.1 ± 0.5 mg (61.2 ± 7.4%), following application to the flank. Overall, the mean apparent dose of rotigotine was

3.59±0.74 mg (53.2 ± 11.0%) which is comparable to values observed in previous clinical trials.

Drug Interaction with CYP2C19 Inhibitor Omeprazole

An open-label, multiple dose trial (**SP862**) investigated the effects of omeprazole (40 mg), a selective inhibitor of CYP2C19, on the steady-state pharmacokinetics of rotigotine transdermal patches (9 mg/20 cm^2) in 54 healthy male subjects, aged 18 to 44 years. All 54 subjects were included in the safety set whereas only 37 subjects were included in the PK set. Trial medication was administered on Days 1 to 14. Subjects received rotigotine 4.5 mg/day (10 cm^2) on Days 1, 2, 3, and 13 and 14 and rotigotine 9.0 mg/day (20 cm^2) on Days 4 to 12. Subjects received omeprazole capsules (40 mg) once daily in the mornings of Days 7 to 12 within 1 minute following patch administration.

Omeprazole co-administration had little effect on the $AUC_{(0\text{-}24h),ss}$ and $C_{max,ss}$ of unconjugated rotigotine. The point estimate for the ratio "rotigotine + omeprazole"/"rotigotine alone" were 0.99 and 1.06 for $AUC_{(0\text{-}24h),ss}$ and $C_{max,ss}$, respectively and the 90% CIs fell within the acceptance range for bioequivalence (0.8;1.25). Similarly, omeprazole co-administration had little effect on the steady-state pharmacokinetics of total rotigotine.

Co-administration of omeprazole had little effect on the $C_{max,ss}$ $AUC_{(0\text{-}24),ss}$, $t_{max,ss}$ and Ae_{ss} of the N-desalkyl metabolites of rotigotine. It must be noted that the plasma concentrations of both metabolites were low and near or below LOQ and therefore the PK parameters were associated with a high degree of variability. In spite of these limitations, the amount of excreted unconjugated rotigotine, total rotigotine as well as its N-desalkyl metabolites did not appear to be altered by omeprazole co-administration.

Population Pharmacokinetics

A study of the population pharmacokinetics of rotigotine in subjects with RLS was based upon data collected from 2 clinical trials, SP790 and SP792 (see *Efficacy* for details).The objectives of the population PK analysis were:

1. To describe population PK characteristics (that is, mean PK parameters) of rotigotine and to characterise the inter- and intra-individual variability of the PK parameters of rotigotine in subjects with RLS.
2. To quantify the relationship between different subject-specific factors (that is, possible covariates such as age, body weight, creatinine clearance [CLcr]) and PK parameters (apparent total body clearance [CL/f], apparent volume of distribution [V/f]).

The final population PK model for rotigotine in subjects with idiopathic RLS receiving different transdermal doses of rotigotine was a one-compartment model with inter-individual variability described on the PK parameters CL/f and V/f. As no adequate characterisation of the absorption phase was given based on the available concentration data in SP790 and SP792, the optional parameter lag time (t_{lag}) was not used for the population PK evaluation. As weight had a large influence on the pharmacokinetics of rotigotine, it (weight/mean weight) was included as a scaling factor for CL/f and V/f in order to minimise variability and to enhance identification of additional covariates. Following characterisation of the base model, the effect of the possible covariates age, sex, body weight, height, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALK), CLcr and total bilirubin on the CL/f and V/f of rotigotine were evaluated by two different methods. Even though body weight was incorporated as a scaling factor, none of these possible covariates was identified as an

additional covariate of CL/f or V/f. Therefore, the base model with weight as a scaling factor on CL/f and V/f was applied as the final model.

For a typical subject with a body weight of 78 kg (mean body weight of the population), the final parameter estimate for CL/f was 502 L/h and for V/f was 121000 L. For CL/f, the results were comparable to the results of other Population PK analyses (for example, SP512: CL/f = 704 L/h, SP513 745 L/h; SP630: CL/f = 1080 L/h). They were also within the same estimated range as reported in several other Phase 1 trials (SP502, SP502, SP581, SP596, SP610, SP626, SP627; range for CL/f = 526 – 1230 L/h). The estimated value for V/f was comparable to the result in the Population PK analysis SP513 (V/f = 145000 L), but was considerably higher than in other studies, for example the population PK evaluation SP630 resulted in a V/f of 2410 L, whereas the model independent PK analysis of trial SP717 had a V/f of 4243 L.

The authors suggest that differences in the above studies can possibly be explained by the fact that SP630 and SP717 used a detailed PK sampling schedule and therefore the rate constant of elimination (k_{el}) may have been more accurately determined than in the present trial and SP513. It must be noted that V/f is the proportional factor between k_{el} and the clearance: CL/f (L/h) = k_{el} (1/h) * V/f (L). Therefore, V/f can only be estimated accurately if the base for kinetics over time can be described appropriately by the measured concentrations. Under steady state conditions the area under the concentration-time curve ($AUC_{ss,\tau}$) during a dosing interval (τ) can be approximated by the following equation using the plasma concentration at steady state (C_{ss}): $AUC_{ss,\tau} = C_{ss} * \tau$. Conversion of the equations results in the following equations: CL/f = Dose / $AUC_{ss,\tau}$ = V/f * k_{el} and V/f = Dose / C_{ss} / τ / k_{el}. With mean levels of C_{ss} of 0.37 ng/mL determined in the present trial for a dose level of 4.5 mg/day a clearance of 507 L/h was calculated, which corresponds to the value obtained in this population PK evaluation. Using a rate constant of elimination of about 0.1/h which has been evaluated in Phase 1 trials, a V/f of 5070 L can be approximated. This calculated value fits very well with the values of V/f reported for trials SP630 and SP717.

Body weight as scaling factor on CL/f and V/f

According to the final model, body weight was identified as a scaling factor of CL/f and V/f. For instance, a 20% increase in body weight resulted in an increase of CL/f and V/f of 20% and approximately 17% lower rotigotine plasma concentrations. By contrast, a 20% decrease in body weight resulted in a decrease of CL/f and V/f of 20% and an approximate 25% increase in rotigotine plasma concentrations. It must be noted that a possible influence of gender on CL/f and V/f may have been indirectly included by the scaling factor, as body weight is generally lower in females than in males. Regarding the estimate of residual variability (residual variability that cannot be explained by the final model, representing a composite of model misspecification, bioanalytical assay variability, intra-individual variability, patient non-compliance etc.), a proportional residual error of 10.8% was determined. Based on the clinical settings of a Phase III trial, the residual error was considered to be low. Therefore, most of the variability could be explained by the final population PK model.

Site of application as a covariate

The additional analysis determined that the site of application alone, and in combination with the BMI, were also covariates, which is consistent with the patch application site influencing the drug absorbance as seen in several studies. Inclusion of the application site resulted in a decrease of the inter-individual variability (IIV) on V/f of 25% compared with the model without application site. Lower absorption leads to a lower exposure and thereby

(considering the nominal dose) to a higher estimated V/f. However, the population PK parameters of rotigotine were estimated in the same range with both models, individually affected by the application sites. The clearance was not affected by the sites of application, the proportionality factor was in the range of 0.9 to 1.19 and the 95% CI included 1. The Volume of Distribution was moderately affected indicating differences in absorption (range 0.5 to 2.76). Most of the records with valid application sites were documented for the application sites of upper arm and shoulder (112 and 51 records). Therefore it is assumed that for these sites the proportionality factor was adequately estimated. The results indicate that there are no differences between the two sites of application. It must be noted that this result contrasts with study SP651 where it was found that application to the shoulder resulted in significantly higher absorption than when the patch was applied to the upper arm. The proportionality factor for the application sites abdomen, thigh and hip was based on a smaller number of valid records (n=28, n=27, and n=22) and should be interpreted as trends only, whereas the application site flank was based on five records only and therefore should not be included in the analysis. The high proportionality factor of thigh indicates a lower absorption. This is in accordance with the results achieved in the pooled analysis of data from trials SP871, SP630, and SP651, investigating the relative bioavailability of rotigotine at different patch application sites. In this analysis, the bioavailability following application at the thigh site was the lowest. The lower proportionality factor for abdomen and hip in the current analysis may indicate higher absorption at these application sites. However, this was not confirmed by the pooled analysis of bioavailability. Given the limited data on different application sites for this population PK analysis, the results from the pooled bioavailability analysis were considered more reliable in estimating differences in rotigotine absorption at different application sites. Regarding efficacy, results of trials SP666 (application site abdomen), SP709 (application site abdomen and flank), and the Phase III trials SP790 and SP792 (rotation of six different application sites) were comparable. Therefore, there appeared to be little clinical relevance associated with the differences in absorption attributable to the different patch application sites.

PK/PD Study Reports

As described in the previous section a double-blind, randomised, placebo- and positive-controlled, parallel-group trial (**SP864**) was conducted to assess the potential electrocardiographic effects of the rotigotine transdermal system at doses up to 120 cm^2/54.0 mg/day in 130 subjects (41 female), aged 29 to 88 years, with advanced-stage idiopathic PD.

In this trial the mean steady-state plasma concentration versus time profiles for both unconjugated (Figure 1) and total rotigotine (Figure 2) showed a similar pattern for each of the sampling days/rotigotine doses (Days 15, 22, 29, 36, and 43 corresponding to doses of 18.0, 27.0, 36.0, 45.0 and 54.0 mg/day). Steady-state levels of rotigotine remained stable over the 24-hour dosing interval. There were dose-proportional increases in $AUC_{(0-24),ss}$ and $C_{max,ss}$ for both unconjugated and total rotigotine.

Figure 1: Mean plasma concentration of unconjugated rotigotine versus time in trial SP864

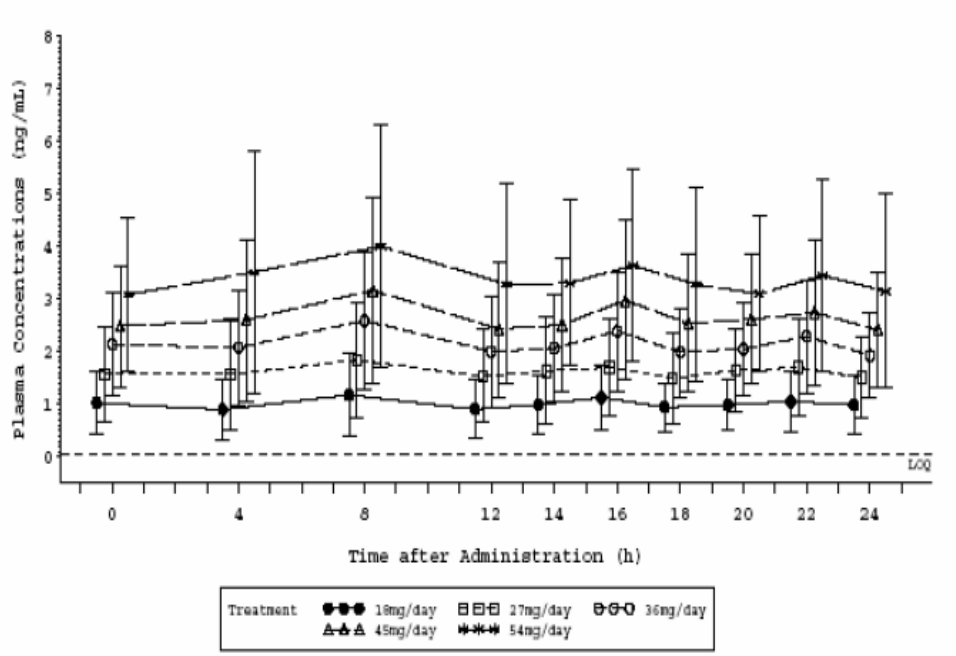
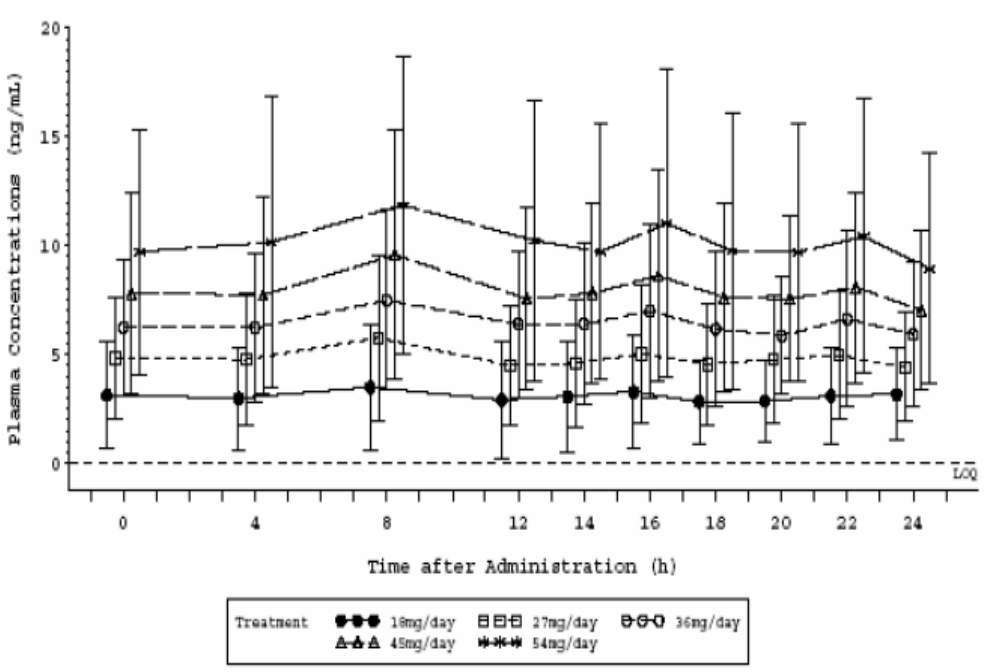

Plasma Concentrations (ng/mL)
0
1
2
3
4
5
6
7
8
LOQ
0
4
8
12
14
16
18
20
22
24
Time after Administration (h)
Treatment
18mg/day
27mg/day
36mg/day
45mg/day
54mg/day

Figure 2: Mean plasma concentration of total rotigotine versus time in trial SP864



The ratio of mean total rotigotine plasma concentrations over mean unconjugated rotigotine plasma concentrations was 3 for all dose levels, indicating that the extent of conjugation was the same over the dose range used in the trial. Plasma concentrations and pharmacokinetic parameters were dose proportional even at supratherapeutic doses. The mean apparent dose of unconjugated rotigotine ranged from 34% to 44% of total administered drug, which was comparable to the apparent dose observed in previous trials in subjects with PD.

No correlation between the plasma concentrations of unconjugated rotigotine and time-matched changes from Baseline in QTcI or QTcIf were evident from this trial.

Summary of PK studies

No new ADME data for the rotigotine transdermal patches were provided in this submission as they were expected to be similar to those observed in the transdermal patches approved for treatment of PD.

The pharmacokinetics of a single rotigotine transdermal patch 6.75 mg/15 cm^2 were bioequivalent with the combined application of 1 x 2.25 mg/5 cm^2 plus 1 x 4.5 mg/10 cm^2 rotigotine patches.

After marketing authorisation, a new polymorphic form of the drug substance rotigotine was identified. The new polymorphic form (Form 2) differed in some of the physicochemical properties from those of the original polymorphic form (Form 1). The $AUC_{(0\text{-}tz)}$ and C_{max} of rotigotine Form 2 and Form 1 were bioequivalent for 10cm^2 patches containing 4.5 mg of each Form.

Oestradiol, LH, and FSH serum concentrations were sufficiently suppressed by a hormonal contraceptive at all time points measured, regardless of whether subjects were treated with 6.75 mg rotigotine or placebo patch. In addition rotigotine had little effect on levonorgestrel

PKs, whereas, the geometric means of $AUC_{(0-24),ss}$ and $C_{max,ss}$ of ethinyloestradiol were slightly higher following rotigotine treatment than placebo.

Co-administration of omeprazole, a selective inhibitor of CYP2C19, had little effect on the PKs of unconjugated and total rotigotine or its N-desalkyl metabolites.

The final population PK model for rotigotine in subjects with idiopathic RLS receiving different transdermal doses of rotigotine was a one-compartment model with inter-individual variability described on the PK parameters CL/f and V/f with weight as a scaling factor. Age and gender were not significant covariates, nor was the site of application. However, for the application sites of abdomen, thigh, hip and flank only a small number of valid records existed (n<28 for each site) and the effects of these application sites on rotigotine pharmacokinetics could not be interpreted reliably.

$AUC_{(0-24),ss}$ and $C_{max,ss}$ increased dose proportionally for both unconjugated and total rotigotine.

No correlation between the plasma concentrations of unconjugated rotigotine and time-matched changes from Baseline in QTcI or QTcIf were identified.

Efficacy

Pivotal Phase III efficacy studies

There were two pivotal Phase III efficacy studies: SP790 and SP792.

SP790

Study design and patient population

This was a multi-centre, randomised, double-blind, placebo-controlled, four-arm parallel-group trial to investigate the efficacy and safety of three different transdermal doses of rotigotine in subjects with idiopathic RLS. It was conducted at 49 sites in 8 countries in Europe during 2005 and 2006. Subjects were randomised into 1 of 4 groups in a 1:1:1:1 ratio to receive placebo, 2.25 mg, 4.5 mg, or 6.75 mg per day rotigotine.

A 7-day run-in period was required for washout of RLS therapy or prohibited concomitant medications and to establish a baseline for the condition. Subjects were up-titrated during the initial 3 week titration period to their designated dose. This was followed by a 6 month maintenance period on a stable dose of rotigotine or placebo. There was a 7 day taper period at the end of the study. Two patches were applied once daily to achieve the designated dose. Patches were applied to the abdomen, thigh, hip, flank, shoulder and/or upper arm on the right or left side. Site of application was rotated daily.

Inclusion into the trial required the diagnosis of idiopathic restless legs syndrome based on the International Restless Legs Syndrome Study Group (IRLSSG) 4 essential criteria (Table 4). In addition subjects needed to have RLS of moderate or severe intensity (score of≥15) as based on the IRLSSG rating scale (IRLS) and be moderately ill as based on the Clinical Global Impressions (CGI) Item 1 (score≥4 points). Subjects need to be aged between 18 and 75 years and have a body mass index (BMI) between 18 and 35 kg/m^2.

Table 4: International Restless Legs Syndrome Study Group Features of Restless Legs Syndrome

A. Essential Criteria	1. Urge to move legs 2. Onset or exacerbation with rest 3. Relief with movement 4. Circadian pattern (worsening at night)
B. Supportive Clinical Features	1. Family history 2. Response to dopaminergic therapy 3. Periodic leg movements
C. Associated Clinical Features	1. Natural clinical course following certain identifiable patterns 2. Sleep disturbance 3. Normal medical evaluation/physical examination

Subjects were excluded from the trial if they had:

- RLS secondary to another condition or medication;
- a history of sleep disturbance from other conditions;
- central nervous system disease;
- prior psychotic episode;
- alcohol or drug abuse;
- renal or hepatic dysfunction;
- malignancy;
- clinically relevant cardiac or peripheral vascular disease;
- symptomatic orthostatic hypotension;
- psychiatric conditions, or
- if pregnant.

Medications which were not allowed during the study were neuroleptics, hypnotics, antidepressants, anxiolytics, benzodiazepines, anticonvulsive therapy, L-dopa, dopamine agonists, opioids, monoamine oxidase (MAO)-inhibitors, catechol-O-methyl transferase (COMT) inhibitors, sedative antihistamines, dopamine antagonist antiemetics (for example, metoclopramide, promethazine), psychostimulatory drugs (for example, amphetamines).

Efficacy endpoints and statistical considerations

The primary efficacy outcome was assessed by the absolute change from baseline to the end of the 6 months maintenance period in the IRLS sum score and the CGI-Item 1 Severity of Illness score. Both variables were included together as primary criteria following feedback from the US FDA.

The main secondary efficacy variables were: IRLS Responder (defined as a subject with a decrease of ≥50% in IRLS sum score from baseline to the end of the maintenance period); CGI-Item 1 Responder (defined as a subject with a decrease of≥50% in CGI-Item 1 at the end of the maintenance period); changes in CGI Items 2 and 3 during the Maintenance Period; change from baseline in individual items on the RLS-6 Rating Scales (a rating of RLS

severity using 6 subscales) at the end of the maintenance period; and the Global Subject Rating of Efficacy.

Clinically significant results were predefined as a reduction of 5 points or more (indicating improvement) in the IRLS sum score and 0.75 points in the CGI Item 1. Based on a 2-group t-test with a 0.025 1-sided significance level, a sample size in each group of 95 subjects was needed to achieve 92% power to detect superiority of rotigotine over placebo for each co-primary endpoint. Each dose was tested hierarchically starting at 6.75 mg/day. The overall power of the trial to demonstrate superiority of all 3 rotigotine doses (6.75, 4.5, and 2.25 mg/day) versus placebo was 61%.

Statistical analysis included an analysis of covariance (ANCOVA) for the changes from baseline to end of the maintenance period with rotigotine dose level or placebo as the main factor, baseline as a covariate, and centre/region/country (if applicable) as a factor. From this ANCOVA, treatment least squares (LS) means (with 95% CI) were calculated and 1-sided 2-sample t-tests were performed (significance level 0.025) to demonstrate superiority of the rotigotine dose level versus placebo, starting with 6.75 mg/day. The corresponding p-values were calculated.

The Full Analysis Set (FAS) with last observation carried forward (LOCF) was considered the primary analysis set for the outcome of the trial. It included all randomized subjects with baseline values and at least one valid post-baseline value under treatment for the primary variables (IRLS sum score and CGI-Item 1). Significant results for both co-primary endpoints were required to demonstrate superiority of the rotigotine dose level over placebo.

Patient disposition, baseline characteristics, compliance

Overall, 549 subjects were enrolled, 91 of whom were not randomised, resulting in 458 randomized subjects. 145 of 458 (32%) prematurely discontinued – 59 (41%) due to lack of efficacy and 56 (39%) due to an adverse event. Lack of efficacy was a more common reason for withdrawal in the placebo group - 37 of 49 withdrawals (76%) - while adverse events were a more frequent cause of withdrawal in the rotigotine groups, 52 of 96 (54%). A major protocol deviation occurred in 65 of 458 (14%) subjects, with a similar incidence in rotigotine and placebo groups and the most common reason being use of prohibited medications. There were 447 subjects included in the FAS.

The mean subject age was 57.6 (range 23 to 78) years and the majority of subjects were female (69% of placebo, 73% of 2.25 mg, 76% of 4.5 mg, and 73% of 6.75 mg rotigotine) and White (99%).

The mean number of years since subjects were diagnosed with RLS was 3.1 years. Overall, 28% of subjects were considered “de novo” (defined as not having received any RLS medication in the last 3 years). At baseline, the mean IRLS sum score was 28.1 for subjects in the placebo group, and ranged from 28.0 to 28.2 across the rotigotine treatment groups. At baseline, the mean CGI Item 1 (Severity of Illness) score was 5.0 for subjects in the placebo group, and ranged from 5.0 to 5.1 across the rotigotine treatment groups. Overall, there were no important differences between treatment groups in the severity of disease at baseline.

Baseline characteristics were similar across groups for concomitant disease and prior medication use. A total of 66% of subjects took a prior anti-Parkinson’s medication—57% of subjects used levodopa (L-dopa) and L-dopa derivatives and 35% used a dopamine agonist. There were no important differences between groups in concomitant medications taken during maintenance period. There were 7 (2%) subjects who concomitantly took anti-Parkinson’s medications, which were considered protocol violations.

The majority of subjects (98% of subjects) in the FAS were considered compliant (defined as ≥85% and <115% compliant) with the trial medication schedule. Treatment compliance was similar across all treatment groups, ranging from 97% to 100%.

Primary efficacy results

There was a dose-related decrease (improvement) in the mean sum score on the IRLS (mean reduction in score of 13.2 to 16.1 points) although relationship between dose and efficacy was not evaluated statistically (Table 5).

Table 5: IRLS sum score at baseline and end of maintenance period in SP790

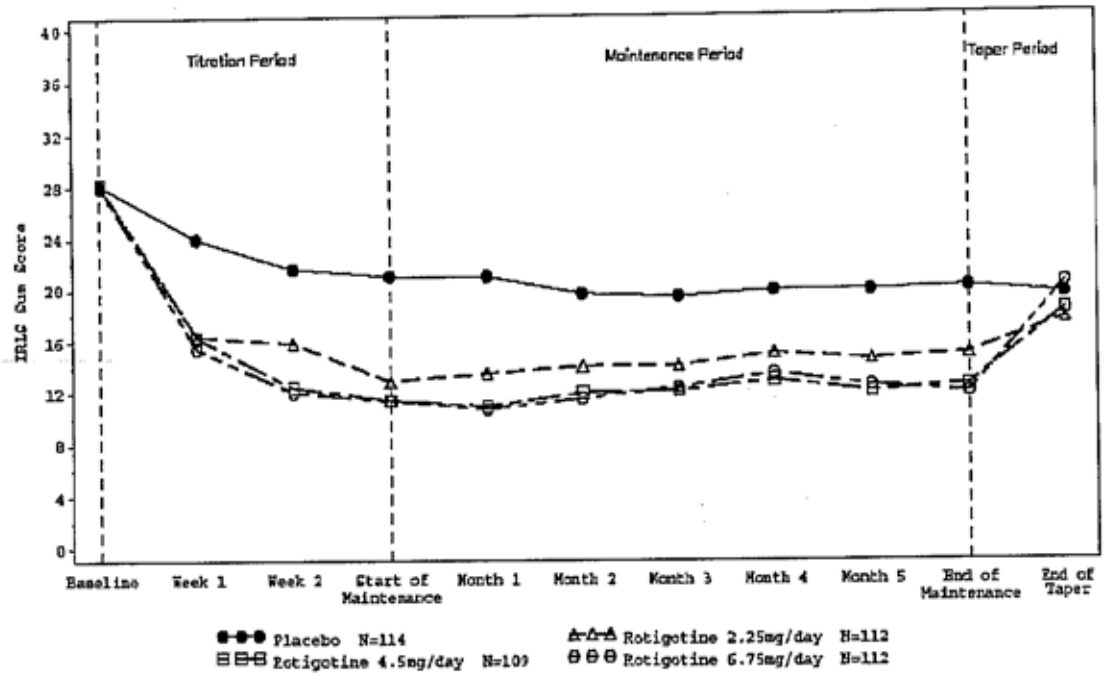
I

Treatment group	n	Mean Baseline IRLS sum score (SD)	Mean IRLS sum score at end of MP (SD)	Mean change from Baseline at end of MP (SD)
Placebo	114	28.1 (6.3)	20.0 (11.2)	-8.0 (9.7)
Rotigotine 2.25mg/day	112	28.1 (6.3)	14.9 (11.1)	-13.2 (10.0)
Rotigotine 4.5mg/day	109	28.2 (6.1)	12.5 (9.6)	-15.6 (9.5)
Rotigotine 6.75mg/day	112	28.0 (5.9)	11.9 (10.9)	-16.1 (10.9)

FAS=Full Analysis Set, IRLS=International Restless Legs Scale, LOCF=last observation carried forward, MP=Maintenance Period, SD=standard deviation

An improvement in the placebo group was also noted (mean reduction in score of 8 points). All rotigotine groups showed improvement in IRLS scores and improvement was maintained during the 6 month treatment period (Figure 3). No clinically meaningful differences between the subgroups (gender, age, region, pre-treatment, and IRLS Baseline severity) were detected. There were 24 (21%) of the placebo group and 22 (7%) of the rotigotine-treated subjects who remained in the very severe symptom group at the end of the maintenance period.

Figure 3: Mean IRLS sum score over time in SP790



A dose-dependent decrease (improvement) in CGI-Item 1 Severity of Illness scores was also observed (a mean reduction of 2.0 to 2.5). A smaller, but still clinically significant, placebo response was also noted (mean reduction of 1.3) (Table 6).

Table 6: CGI Item 1 at baseline at end of maintenance period in SP790

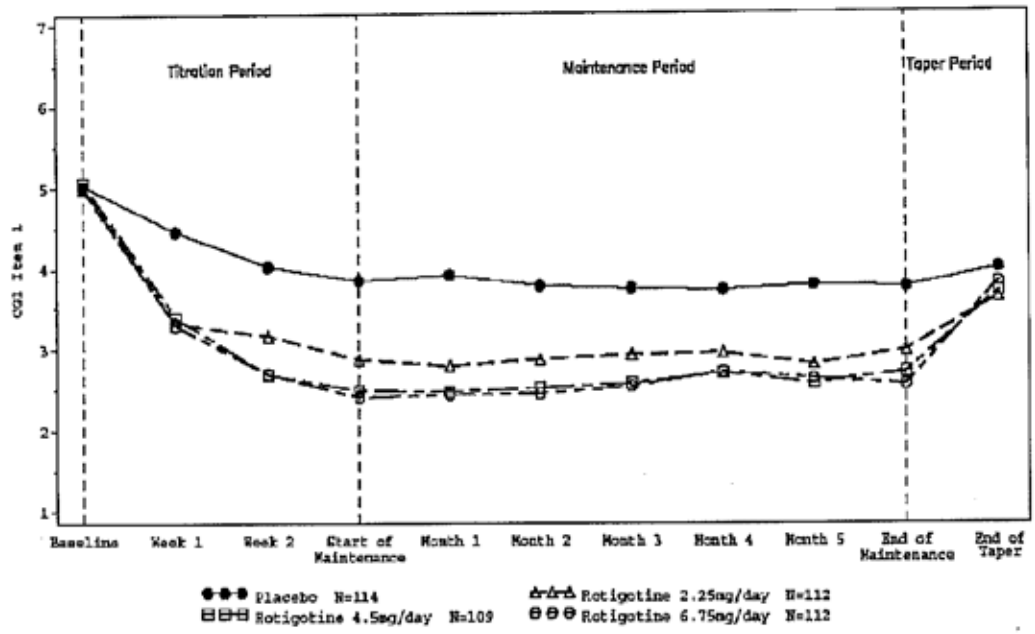
C(

Treatment group	n	Mean Baseline CGI Item 1 score (SD)	Mean CGI Item 1 score at end of MP (SD)	Mean change from Baseline at end of MP (SD)
Placebo	114	5.0 (0.8)	3.8 (1.7)	-1.3 (1.5)
Rotigotine 2.25mg/day	112	5.0 (0.9)	3.0 (1.6)	-2.0 (1.6)
Rotigotine 4.5mg/day	109	5.1 (0.8)	2.7 (1.3)	-2.4 (1.4)
Rotigotine 6.75mg/day	112	5.0 (0.8)	2.6 (1.4)	-2.5 (1.5)

CGI=Clinical Global Impressions, FAS=Full Analysis Set, LOCF=last observation carried forward, MP=Maintenance Period, SD=standard deviation

Thirteen of 333 (4%) rotigotine-treated subjects were considered severely ill at the end of the maintenance period compared to 21 of 114 (18%) placebo-treated subjects. Graphical representation of CGI-Item 1 data also shows a maintained improved over the treatment duration and onset of action during the titration period (Figure 4). No clinically meaningful differences between the subgroups (gender, age, region, pre-treatment, and IRLS baseline severity) were detected.

Figure 4: Mean CGI Item 1 score over time in SP790



Treatment difference (rotigotine to placebo) for both primary endpoints was statistically significant for each of the three dose groups.

Secondary efficacy results

Table 7 summarises the proportion of IRLS and CGI-Item 1 Responders by treatment group. Around 50 to 60% of rotigotine-treated subjects responded to treatment by this definition compared to 25 to 30% of placebo-treated subjects. Analysis of CGI-Item 3 Therapeutic

Effect showed that 239 of 307 (78%) rotigotine-treated had a moderate or very good therapeutic effect, while 41 of 307 (15%) had no response or worsened. Each item of the RLS-6 Rating Scales was examined and reductions in all individual items were seen for all rotigotine doses. More modest reductions in these subscales were seen in the placebo group though the difference was not tested statistically.

To assess IRLS Remitters, scores on the IRLS of ≤10 or 0 at the end of the maintenance period were examined; 79 of 333 subjects (24%) rotigotine-treated subjects had an IRLS sum score of 0 compared to 12% of placebo-treated subjects.

Table 7: Co-primary endpoint responder analysis in SP790

Treatment group	Number of responders n/N (%)	Treatment difference vs placebo
IRLS		
Placebo	29/114 (25.4)	--
Rotigotine 2.25mg/day	58/112 (51.8)	26.3
Rotigotine 4.5mg/day	63/109 (57.8)	32.4
Rotigotine 6.75mg/day	62/112 (55.4)	29.9
CGI Item 1		
Placebo	36/114 (31.6)	--
Rotigotine 2.25mg/day	57/112 (50.9)	19.3
Rotigotine 4.5mg/day	58/109 (53.2)	21.6
Rotigotine 6.75mg/day	69/112 (61.6)	30.0

CGI=Clinical Global Impressions, FAS=Full Analysis Set, IRLS=International Restless Legs Scale, LOCF=last observation carried forward

Summary

The study demonstrated efficacy at the three doses (2.25 mg, 4.5 mg and 6.75 mg/day) that was dose-dependent. The onset of action was seen after 1 week and was maintained during the 6 months of treatment. Despite an evident placebo response, results were statistically significant and supported by secondary efficacy endpoints.

SP792

Study design and patient population

This was a multi-centre, randomised, double-blind, placebo-controlled, 5-arm parallel-group trial to investigate the efficacy and safety of 4 different transdermal doses of rotigotine in subjects with idiopathic RLS. It was a similar design to SP790 except that subjects were randomised into 1 of 5 groups (rather than 4) in a 1:1:1:1:1 ratio to receive placebo, 1.125 mg, 2.25 mg, 4.5 mg, or 6.75 mg per day rotigotine, the additional group being the lower dose of 1.125 mg/day. This dose was included to establish a minimum effective dose as per feedback from the US FDA. The study was conducted in the USA and involved 58 sites.

The design was the same as SP790 with a 7-day run-in period, a 4 week titration period (one week longer due to the added lower dose), 6 months of maintenance therapy and a 7 day taper period at the end. There were 2 patch sizes used to deliver the designated dose, 1.125 mg (2.5 cm^2) or 4.5 mg (10 cm^2) of rotigotine, with subjects applying 3 patches per day during the maintenance period. Patch application site was rotated daily as per study SP790.

Inclusion and exclusion criteria were the same as SP790.

Efficacy endpoints and statistical considerations

Primary and secondary efficacy outcome variables were the same as in SP790. The sample size and power calculation were the same as SP790, that is, 95 subjects were needed per treatment group to give a 92% power to detect superiority of rotigotine over placebo. Statistical analysis was the same as SP790.

Patient disposition, baseline characteristics, compliance

There were 811 subjects enrolled in the study, 306 of whom were not randomised (reportedly for consent withdrawal), resulting in 505 randomized subjects. There were a similar high number of subjects failing to complete the study as in SP790, with 185 of 505 (37%) who prematurely discontinued. Of these premature discontinuations 78 (42%) were due to adverse events, 27 (15%) due to lack of efficacy, and 33 (18%) due to consent withdrawal. The most common reason for discontinuation in the placebo group was lack of efficacy (8 of 33, 24%) and in the rotigotine group was adverse events (75 of 152, 49%).

A major protocol deviation occurred in 107 of 505 (21%) subjects, and was similar in placebo and rotigotine groups except for the 6.75 mg group where the rate was 26.4%. The most common reason for protocol deviation was dosing compliance violation. There were 494 subjects included in the FAS.

The mean subject age in this study was slightly younger (52.3 years) than in study SP790 (57.6 years). The majority of subjects were female (60.7%) with a similar proportion across placebo and rotigotine groups, and 94% of subjects were Caucasian.

The mean number of years since subjects were diagnosed with RLS was 2.1 years. Overall there were more subjects considered “de novo” than in SP790 (64% versus 28%). At baseline, the mean IRLS sum score was 23.5 for subjects in the placebo group, and ranged from 23.1 to 23.6 across the rotigotine treatment groups. At baseline, the mean CGI-Item 1 (Severity of Illness) score was 4.7 for subjects in the placebo group, and ranged from 4.6 to 4.7 across the rotigotine treatment groups. There were no important differences between treatment groups in the severity of disease at baseline. Overall the subjects in SP792 had slightly less severe disease and of shorter duration than subjects in SP790.

Treatment groups were similar with respect to concomitant medical conditions and medication use both prior and during the study. A total of 21% of subjects took a prior anti-Parkinson’s medication compared to 66% in SP790. There were 3 (<1%) subjects who concomitantly took a dopamine agonist. Other baseline characteristics were similar across treatment groups.

Overall, 93% of subjects in the FAS were considered compliant (defined as ≥85% and <115% compliant) with the trial medication schedule. Treatment compliance was similar across all treatment groups, ranging from 90 to 96%.

Primary efficacy results

As with SP790, there was a dose-dependent decrease (improvement) in the mean sum score on the IRLS (mean reduction in score of 10.9 to 14.3 points). An improvement in the placebo group was also noted (mean reduction in score of 9 points) (Table 8).

Table 8: IRLS sum score at baseline and end of maintenance period in SP792

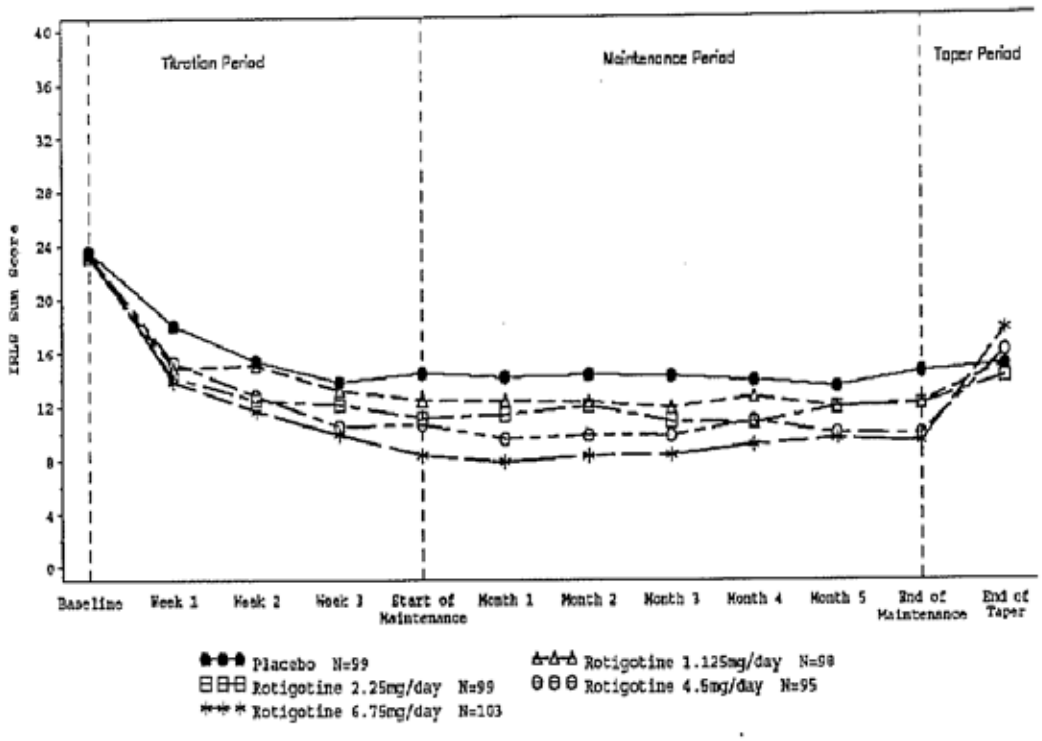
IR

Treatment group	n	Mean Baseline IRLS sum score (SD)	Mean IRLS sum score at end of MP (SD)	Mean Change from Baseline at end of MP (SD)
Placebo	99	23.5 (5.1)	14.5 (8.0)	-9.0 (7.7)
Rotigotine 1.125mg/day	98	23.1 (5.0)	12.2 (8.2)	-10.9 (8.9)
Rotigotine 2.25mg/day	99	23.2 (5.3)	12.1 (8.7)	-11.1 (9.3)
Rotigotine 4.5mg/day	95	23.3 (4.6)	9.9 (8.8)	-13.4 (9.2)
Rotigotine 6.75mg/day	103	23.6 (5.0)	9.3 (8.5)	-14.3 (9.4)

FAS=Full Analysis Set, IRLS=International Restless Legs Syndrome Study Group Scale, LOCF=last observation carried forward, MP=Maintenance Period, SD=standard deviation

All rotigotine groups showed improvement in IRLS scores and improvement was maintained during the 6 month treatment period (Figure 5). Onset of action was noted to occur during the titration period. No clinically meaningful differences between the subgroups (gender, age, race, region of USA, pre-treatment, and IRLS Baseline severity) were detected. There were 25 (25%) of the placebo group and 58 (15%) of the rotigotine-treated subjects who remained in the severe or very severe symptom group at the end of the maintenance period.

Figure 5: Mean IRLS sum score over time in SP792



The CGI-Item 1 Severity of Illness scores showed greater improvement with the higher rotigotine doses (4.5 and 6.75 mg/day) compared to the lower doses although a definite dose-

efficacy relationship was not established statistically. However a clinically meaningful difference over placebo was only seen with the highest rotigotine dose (6.75 mg/day) (Table 9).

Table 9: CGI Item 1 at baseline at end of maintenance period in SP792

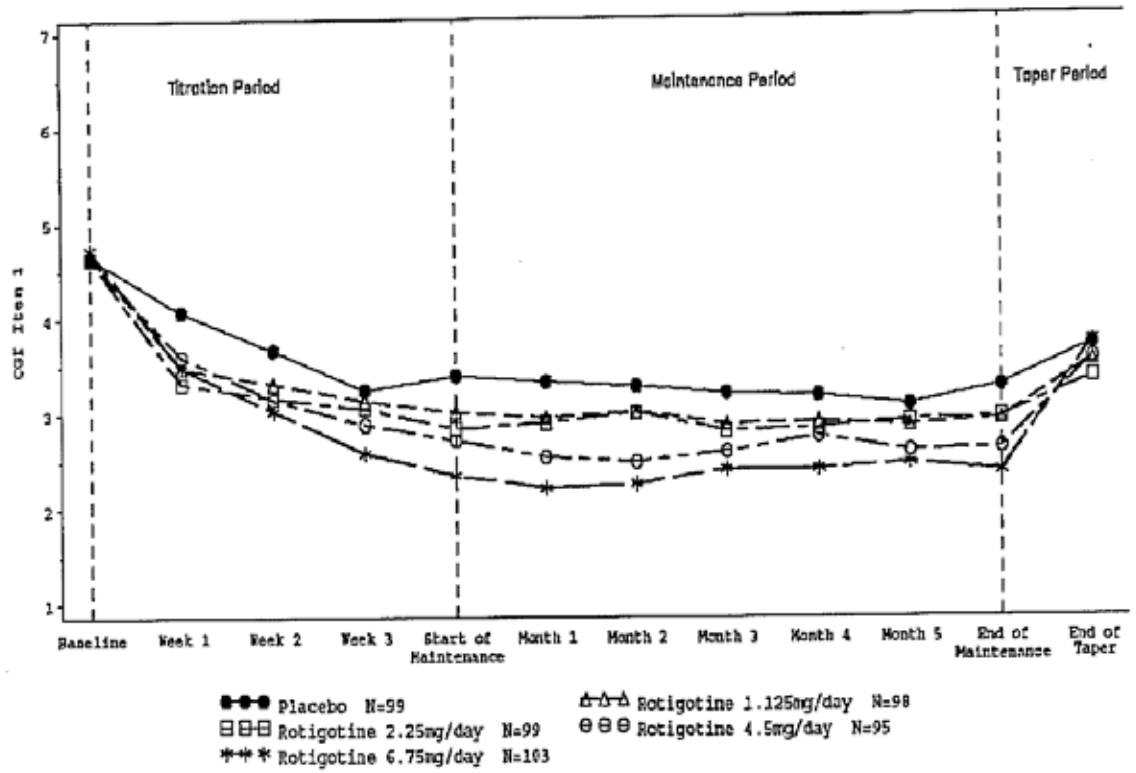
C(

Treatment group	n	Mean Baseline CGI Item 1 score (SD)	Mean CGI Item 1 score at end of MP (SD)	Mean change from Baseline at end of MP (SD)
Placebo	99	4.7 (0.6)	3.3 (1.2)	-1.4 (1.2)
Rotigotine 1.125mg/day	98	4.7 (0.8)	2.9 (1.3)	-1.8 (1.5)
Rotigotine 2.25mg/day	99	4.6 (0.7)	2.9 (1.4)	-1.7 (1.5)
Rotigotine 4.5mg/day	95	4.7 (0.8)	2.6 (1.4)	-2.0 (1.5)
Rotigotine 6.75mg/day	103	4.7 (0.8)	2.4 (1.3)	-2.4 (1.5)

CGI=Clinical Global Impressions; FAS=Full Analysis Set, LOCF=last observation carried forward, MP=Maintenance Period, SD=standard deviation

Eight of 395 (2%) rotigotine-treated subjects were considered severely ill at the end of the maintenance period compared to 4 of 99 (4%) placebo-treated subjects. Graphical representation of CGI Item 1 data also shows maintained improved over the treatment duration and onset of action during the titration period (Figure 6). No clinically meaningful differences between the subgroups (gender, age, region, pre-treatment and IRLS Baseline severity) were detected.

Figure 6: Mean CGI Item 1 score over time in SP792



Only the two higher doses of rotigotine (4.5 mg/day and 6.75 mg/day) demonstrated statistically significant improvement over placebo on the two co-primary endpoints (IRLS sum score and CGI Item 1) (Table 10). Treatment difference was not statistically significant for the two lower doses (1.125 mg/day and 2.25 mg/day). This is in contrast to study SP790 where the 2.25 mg/day dose of rotigotine was statistically significantly better than placebo.

Table 10: ANCOVA results for co-primary endpoints: change from baseline to end of maintenance period in SP792

AN

Variable	Treatment (n)	LS mean	Treatment difference vs placebo	2-sided p-value
IRLS sum score	Placebo (99)	-9.0	--	--
	Rotigotine 1.125mg (98)	-11.1	-2.2	0.0682
	Rotigotine 2.25mg (99)	-11.2	-2.3	0.0535
	Rotigotine 4.5mg (95)	-13.5	-4.5	0.0002
	Rotigotine 6.75mg (103)	-14.2	-5.2	<0.0001
CGI Item 1	Placebo (99)	-1.40	--	--
	Rotigotine 1.125mg (98)	-1.75	-0.35	0.0603
	Rotigotine 2.25mg (99)	-1.72	-0.32	0.0857
	Rotigotine 4.5mg (95)	-2.05	-0.65	0.0007
	Rotigotine 6.75mg (103)	-2.31	-0.90	<0.0001

ANCOVA=analysis of covariance, CGI=Clinical Global Impression, FAS=Full Analysis Set, IRLS=International Restless Legs Syndrome Study Group Rating Scale, LOCF=last observation carried forward, LS mean=least squares means

Secondary efficacy results

Around half of rotigotine-treated subjects were classified as Responders (57% on the IRLS and 50% on CGI-Item 1). For placebo-treated subjects, the proportion of responders was 37% on IRLS and 30% on CGI-Item 1 (Table 11). As with SP790, 73% (236/323) of subjects treated with rotigotine were found to have a moderate or very good therapeutic effect based on the CGI-Item 3 Therapeutic Effect. However, 15% of the rotigotine-treated patients had no response or worsened.

Table 11: Co-primary endpoint responder analysis in SP792

Treatment group	Number of responders n/N (%)	Treatment difference vs placebo
IRLS		
Placebo	37/99 (37)	--
Rotigotine 1.125mg/day	47/98 (48)	10.6
Rotigotine 2.25mg/day	51/99 (52)	14.1
Rotigotine 4.5mg/day	57/95 (60)	22.6
Rotigotine 6.75mg/day	69/103 (67)	29.6
CGI Item 1		
Placebo	30/99 (30)	--
Rotigotine 1.125mg/day	40/98 (41)	10.5
Rotigotine 2.25mg/day	46/99 (47)	16.2
Rotigotine 4.5mg/day	50/95 (53)	22.3
Rotigotine 6.75mg/day	61/103 (59)	28.9

CGI=Clinical Global Impression, FAS=Full Analysis Set, IRLS=International Restless Legs Syndrome Study Group Rating Scale, LOCF=last observation carried forward

Reductions across all individual items on the IRLS were noted, except for Item 5 severity of symptoms during the day when engaged in activities. The proportion of subjects with an IRLS sum score of 0 at the end of the maintenance period was higher in the rotigotine groups (16%, 17%, 30%, and 29% in the 1.125 mg, 2.25 mg, 4.5 mg and 6.75 mg/day groups respectively) compared to the placebo group (9%), however this difference was not tested statistically.

Summary

This trial demonstrated a trend for dose dependent response across the rotigotine groups; however superiority over placebo was demonstrated only in the 2 higher dose groups (4.5 mg and 6.75 mg/day). Baseline severity of disease and prior treatment are seen to influence treatment response with a greater improvement in those more severely affected or who had received prior therapy. Compared to SP790, this study's subjects had less severe RLS of shorter duration and with less prior anti-Parkinson's treatment and this may explain why the 2.25 mg/day dose was not effective in this trial. As in trial SP790, an onset after one week and maintenance of action over a 6 month period were seen.

Efficacy in subgroups

As trials SP790 and SP792 had identical endpoints, and no important differences in inclusion and exclusion criteria, data were pooled for analysis of efficacy in subgroups (Pool RE1). This pool contained 941 subjects of whom 307 (33%) discontinued. There were a greater number of discontinuations were due to adverse events in the rotigotine group (16% compared to 3% of placebo) while a greater number of discontinuations in the placebo group were due to lack of efficacy (21% compared to 5% of rotigotine). Average age of randomised subjects was 54.9 years, 25% were over 65 years, 66% were female and 97% were white. The mean body mass index was 27 kg/m^2, (26% had a BMI of $\geq$30 kg/m^2); 58% consumed alcohol and 17% used tobacco. Treatment groups were similar with respect to baseline disease severity, 47% of subjects had not received RLS medication in the prior 3 years.

Effect of age, gender, race and BMI

Based on IRLS sum score, rotigotine treatment response was greater in subjects aged <65 years (net treatment difference over placebo of -3.6 to -7.8 compared to 1.7 to -3.9 in those aged ≥65 years). The placebo response was slightly greater in those aged ≥65 years (-10.1 compared to -7.8 in <65 years). When assessing treatment response based on CGI-Item 1, a less pronounced effect in the subjects aged <65 years was seen (net treatment difference was -0.56 to -1.21, compared to -0.04 to -0.74 in ≥65 years).

Treatment response was higher in females than males across all dose groups as based on the IRLS sum score. However this difference was not as apparent when based on CGI-Item 1 score.

Almost all subjects who were pooled from the primary efficacy trials were White (909/941, 97%), and only a small number were Black (9/941, 1%), Asian (3/941, <1%), or of other races (20/941, 2%). Therefore, no efficacy conclusions can be drawn with respect to differences in race from the primary efficacy trials.

There were no obvious trends in treatment response based on IRLS sum score or CGI-Item 1 for subjects of BMI 18.5 to <25, 25 to <30, or ≥30.

Effect of baseline disease severity

Treatment response as measured by change in mean IRLS sum score was most pronounced in subjects with severe or very severe RLS compared to moderate RLS at Baseline. This increased response in the more severely affected subjects was also seen when measured by CGI-Item 1. Treatment response as measured by change in mean IRLS sum score was more pronounced in rotigotine-treated subjects who had received previous RLS treatment than in "de novo" subjects.

Alcohol and tobacco use

There were no obvious differences in treatment response between subjects who did or did not consume alcohol or use tobacco (as based either on the IRLS sum score or CGI-Item 1).

Supporting studies

SP666

Study design and patient population

SP666 was a multicentre, double-blind, randomized, placebo-controlled, four-arm, parallel-group trial of rotigotine in patients with idiopathic RLS (Phase IIa). It was designed to show proof-of-concept and to analyse the dose-response relationship and assess safety and tolerability of rotigotine in subjects with moderate to severe idiopathic RLS. The trial was conducted at 9 sites in Germany during 2001 and 2002. The trial design included a 7 day washout period and a one week randomised treatment period. There were 3 rotigotine dose groups 1.125 mg, 2.2.5 mg and 4.5 mg and a placebo group randomised in a 1:1:1:1 ratio.

Subjects were aged 18 to 75 years and had a diagnosis of RLS as per the 4 essential features and a minimum score of≥5 on the IRLS Sum score if on L-dopa, or ≥10 if untreated, and a score of ≥3 for severity of RLS during the day. Subjects also needed to show response to treatment with dopaminergic medication if they had previously received this treatment. Subjects were excluded if they had symptoms only at night. Other exclusion criteria were the same as for the previously discussed trials.

Efficacy endpoints and statistical considerations

The primary endpoint was the absolute change from baseline to end of treatment in the IRLS sum score, comparing three doses of rotigotine with placebo. As this was a pilot study no sample size nor power calculations were carried out. A sample size of 40 was chosen for practical reasons (time frame and limited number of study sites). Descriptive analyses were carried out with the FAS, giving summary statistics, 95% confidence intervals and p-values, in conjunction with an analysis of covariance model (ANCOVA), where treatment groups were included as the main factor and baseline IRLS score as a covariate.

Patient disposition, baseline characteristics and compliance

There were 68 subjects enrolled and 63 randomised. The full analysis set comprised 63 subjects. One subject withdrew prematurely due to an adverse event and there were 4 subjects with major protocol deviations resulting in 58 subjects in the per-protocol set. The mean age of subjects was 58.3 years, 98% Caucasian, and 63.5% were female. The severity of disease was similar amongst groups and the level of severity on the IRLS was on average "Severe" with a mean score of 26. Prior treatment for RLS had been taken by 87.3% of subjects.

Results

Improvements in all three active treatment groups, as based on change in the IRLS sum score, were seen and were larger than that in the placebo group. Reductions in mean score from baseline for each group were: 8.0, 10.5, 12.3 and 15.7 in the placebo, 1.125 mg, 2.25 mg and 4.5 mg/day rotigotine groups respectively. However, only the 4.5 mg/day dose group was statistically significantly better than placebo (p=0.0095). Significant improvement over placebo was noted for the highest dose (4.5 mg) on all 6 items in the IRLS scale.

Overall, the study showed that a dose of 4.5 mg/day of rotigotine could reduce RLS symptoms at a clinically meaningful level (net effect over placebo of 7.7 points). Results also suggested a dose response.

SP709

Study design and patient population

This was a Phase IIb multi-centre, double-blind, randomized, placebo-controlled, six-arm, parallel-group, dose-finding trial to determine efficacy, safety and tolerability of five different transdermal doses of rotigotine (1.125 mg, 2.25 mg, 4.5 mg, 6.75 mg, and 9.0 mg) in 341 subjects with idiopathic RLS. Following on from positive results with 4.5 mg in the Phase IIa (SP666) trial, two higher doses (6.75 mg and 9.0 mg/day) were included in this trial for further investigation. Subjects were randomised to receive placebo or rotigotine in a 1:1:1:1:1:1 ratio. The trial was undertaken at 34 sites in 3 countries in Europe and occurred in 2003 to 2004. The trial consisted of a 2 week titration period, a 4 week maintenance period, and a 1 week taper period. Patches were applied daily to the right or left, upper or lower abdomen, and flank.

Adult subjects were included with a diagnosis of idiopathic RLS and a minimum IRLS sum score ≥15 at baseline. Exclusion criteria were similar to those already discussed in the Phase III, pivotal studies.

Efficacy endpoints and statistical considerations

The primary efficacy variable was absolute change in the IRLS sum score from baseline to the end of the maintenance period. With a sample size of 35 subjects per treatment group the study had a power of 80% to detect a difference between the placebo and the 9.0 mg

rotigotine group assuming a mean change in IRLS sum score of 7.0 points with a standard deviation of about 10.0 using a 1-sided 2-sample t-test with significance level 0.025.

Patient disposition, baseline characteristics and compliance

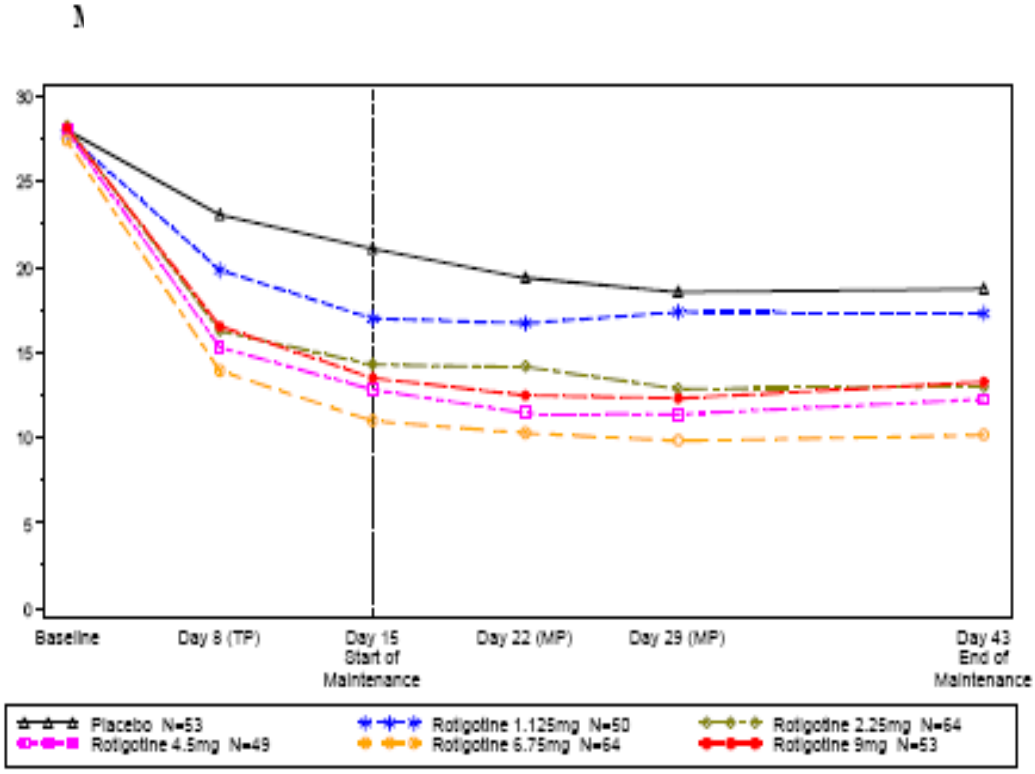
There were 371 subjects enrolled with 341 randomised. Of these subjects, 31 (9%) prematurely discontinued the trial, the most common reason for which was an adverse event in 15 subjects (4% of all randomised). Major protocol deviations occurred in 44 of 341 (13%) of subjects and the proportion was similar across treatment groups. The FAS consisted of 333 subjects (98% of randomised). Treatment compliance was 96% for placebo and 94% for all rotigotine subjects.

The mean subject age was 58.4 years, all were Caucasian, and the majority were female (placebo 62%, rotigotine 68%). Subjects had a long history of disease (17 years since symptom onset and 3 years since diagnosis) with 79% reporting previous response to dopaminergic medication. Characteristics were similar across treatment groups. At baseline, the mean IRLS sum score was 28.0 for placebo subjects and between 27.4 and 28.0 for the rotigotine groups. There were similar proportions across groups for prior diseases and medication use. Overall, 271 patients (80%) were taking a dopaminergic medication prior to study treatment. Washout of dopamine agonists was required prior to study treatment.

Results

The mean change from baseline to end of maintenance period is shown in Figure 7.

Figure 7: Mean IRLS sum score during treatment phase in SP709



TP=Titration Period, MP=Maintenance Period

The treatment difference between rotigotine and placebo at the end of the maintenance period was statistically significant for all rotigotine doses except the lowest dose of 1.125 mg/day. The largest improvement was in the 6.75 mg/day group. The dose dependent effect did not extend to the 9.0 mg/day dose which did not show greater symptom reduction than the 6.75

mg/day dose. There was correlation between the IRLS sum score and the CGI-Item 1 score with the overall correlation coefficient for the FAS being 0.8012.

Secondary efficacy analyses were consistent with the primary efficacy results. The individual items on the RLS scale (6 subscales) showed greater decrease (improvement) with the doses 2.25 mg, 4.5 mg, 6.75 mg and 9.0 mg than the 1.125 mg. There is also some drop off in improvement with the highest dose (9.0 mg) compared to the 6.75 mg dose.

Positive treatment efficacy was observed with rotigotine doses of 2.25 mg to 9.0 mg/day. The lowest dose 1.125 mg/day was not superior to placebo and the greatest improvement was observed in the 6.75 mg/day group (mean decrease in IRLS sum score of 17.3, or 8.3 points over placebo). There was a noted placebo effect (-9.3 points on IRLS sum score). The minimum effective dose appears to be 2.25 mg/day and the maximal effective dose is 6.75 mg/day with no further improvement at 9.0 mg/day dose.

SP794

Study design and patient population

This was a multicentre, double-blind, randomized, placebo-controlled, two-arm, parallel-group, sleep laboratory trial to investigate the efficacy and safety of transdermal rotigotine in subjects with idiopathic RLS. This study was conducted in 2005 and 2006 in Europe. Subjects were randomised to receive rotigotine or placebo in a 2:1 ratio. The objective of this trial was to demonstrate that rotigotine is effective in subjects with idiopathic RLS based on the Periodic Limb Movement Index (PLMI = PLMs/total time in bed [TIB]) as measured by polysomnography (PSG).

After a run-in period to wash out previous treatment, there was a 3 week titration period with weekly increases of rotigotine/placebo dose to reach the optimal dose, from an initial dose of 2.25 mg/day to a maximum dose of 6.75 mg/day. There was then a 4 week maintenance period and a 7 day taper period. Sleep laboratory measurements were performed during the 2 consecutive nights prior to the baseline visit and prior to the end of the maintenance period. A single patch of 2.25 mg, 4.5 mg/day, or 6.75 mg/day was applied daily with the site being rotated.

The study included subjects with the diagnosis of idiopathic RLS who also satisfied the following criteria: (1) either had no previous treatment for RLS or have had initial response to previous dopaminergic treatment; (2) have a score of IRLS score of≥15 at baseline; (3) CGI-Item I score of ≥4 points at baseline; and (4) have a Periodic Limb Movement Index (PLMI; periodic limb movements [PLMs]/total time in bed [TIB]) of ≥15 based on polysomnography (PSG) as assessed by the investigator. As with the other trials, subjects were aged 18 to 75 years with a BMI 18 to 35 kg/m^2. Exclusion criteria were the same as in previous trials.

Efficacy endpoints and statistical considerations

The primary efficacy outcome was assessed by the reduction of the PLMI at the end of the maintenance period compared to baseline. PLMI (PLMs/TIB) data was obtained from PSGs which were evaluated at a central reading laboratory.

The following secondary variables were measured as change from baseline at the end of the maintenance period: PLMSAI (Periodic Limb Movements during Sleep Arousal Index = PLMs during sleep with arousals/total sleep time); Sleep efficiency (%; sleep time/TIB); IRLS sum score, CGI-Item 1 (Severity of Illness); and Medical Outcomes Study (MOS) Sleep Scale-Adequacy Subscale.

The primary analysis was an analysis of covariance (ANCOVA) of the log-transformed PLMI at the end of the maintenance period. A sample size of 51 subjects using an active:placebo allocation of 2:1 (34 active and 17 placebo) was required to provide 90% power to demonstrate superiority of rotigotine over placebo, assuming that a 2-fold change in means was detected, and that the coefficient of variation was 0.8 using a two-group t-test with a 0.025 one-sided significance level. The FAS included all subjects who are randomized, had at least 1 dose of trial medication, had a valid baseline assessment, and at least 1 valid post dose assessment.

Patient disposition, baseline characteristics, and compliance

There were 96 subjects enrolled and 67 were randomised to receive treatment. There were 6 premature discontinuations – 3 due to an adverse effect (AE), 2 withdrew consent and 1 withdrew due to lack of efficacy. At least one major protocol deviation was recorded in 9 of 67 (13%) subjects, the most common being prohibited concomitant medication use and dosing compliance violation.

There were 66 subjects included in the primary analysis - 20 received placebo and 46 rotigotine. The mean age of subjects was 59.1 years, the majority were female (67% placebo, 76% rotigotine) and all were Caucasian. The mean number of years since RLS diagnosis was 2.2 years, 42% of subjects had not received RLS medication in the last 3 years. Severity of disease was similar between groups at baseline. Concomitant disease was similar between groups. Prior anti-Parkinson's medication was taken by 9 (43%) of the placebo group and 26 (57%) of the rotigotine group.

Compliance with treatment (as previously defined) was recorded for 95% of placebo and 96% of rotigotine subjects. During the maintenance period, 12 subjects received 2.25 mg/day, 18 received 4.5 mg/day and 16 received 6.75 mg/day.

Results

There was a reduction in the geometric mean PLMI from baseline to end of maintenance in both groups, though the effect was larger in the rotigotine group - from 37.4 to 27.1 for placebo group and from 50.9 to 8.1 in the rotigotine group (Table 12). Rotigotine was 4.25 times more effective than placebo in the reduction of the PLMI at the end of the Maintenance Period (95% CI for the ratio 2.48 to 7.28, p<0.0001). A total of 39% and 68% of rotigotine-treated subjects had a reduction in PLMI to <5 and <15, respectively, at the end of the maintenance period. No placebo-treated subjects had a reduction in PLMI to <5, and 20% of placebo-treated subjects had a reduction to <15 at the end of the maintenance period.

Table 12: PLMI at baseline and end of maintenance period in SP794

Treatment group	n	Geometric Mean Baseline PLMI	CV (%)	Geometric mean PLMI at end of MP	CV (%)
Placebo	20	37.4	72.4	27.1	101.5
Rotigotine	41	50.9	60.8	8.1	167.0

CV=coefficient of variation, FAS=Full Analysis Set, MP=Maintenance Period, PLMI=Periodic Limb Movement Index, SD=standard deviation

Gender, age, prior use of a dopamine agonist, or severity of disease did not affect a subject's reduction in the PLMI, regardless of treatment group.

An index of PLMs resulting in arousal during sleep (Periodic Limb Movements during Sleep Arousal Index, PLMSAI) was reduced to a clinically normal level of≤2 in 73% (30/41) of rotigotine-treated subjects compared to 25% (5/20) of placebo-treated subjects. A treatment difference of 3.12 (p-value=0.0072) in favour of rotigotine was observed in an ANCOVA analysis. IRLS sum score at the end of the maintenance period showed a statistically significant mean change in the rotigotine group compared to the placebo group (net treatment difference -6.1, 95% CI -10.7 to -1.47, p=0.01).

The Medical Outcomes Study (MOS) Sleep Scale is a 12 item sleep questionnaire (Hays & Stewart 1992) which combines the analysis of subject ratings on "get enough sleep to feel rested in the morning" and "get amount of sleep needed" questions.[7] Interestingly, despite the reduction in limb movements, there was no treatment difference noted on this scale (LS means for placebo was 15.62, and for rotigotine was 15.29).

Overall, rotigotine significantly reduced motor symptoms of RLS during sleep compared to placebo, however, no significant effect was seen on overall sleep quality.

Long term efficacy

Three open label extension studies in RLS (SP710, SP791 and SP793) were used to assess long term efficacy of rotigotine.

SP710

As the final study report was not available, data were supplied in 3 interim reports: Year 1, Year 2 and Year 3 (patient data to February 2007).

Study design and patient population

This was an open label extension trial to determine safety and tolerability of long-term transdermal application of rotigotine in subjects with idiopathic RLS. It is an extension of the Phase IIb study (SP709). It was conducted at 33 sites in Europe (Austria, Germany and Spain). The trial commenced mid 2003 and planned to run for 5 years or until rotigotine is commercially available.

Upon entering SP710, subjects completed a titration period of up to 4 weeks where subjects were up-titrated in weekly 2.25 mg/day increments until reaching their optimal dose. Subjects then entered a maintenance period of up to 5 years, and ended the study with a 1-week taper period, and a 2-week safety follow-up period.

Trial medication was administered as a transdermal patch once daily, initially as a combination of 1, 2 or 3 patches, but after a protocol amendment as a single dose patch. The dose of rotigotine (1.125 mg, 2.25 mg, 4.5 mg, 6.75 mg, and 9 mg) was determined individually for each subject based on the CGI Item 3 (therapeutic effect) and Item 4 (side effects) score. The investigator was able to alter a subject's dose during the maintenance period if felt necessary. Patches were applied to one of the following application sites: right or left side of the upper or lower abdomen, thigh, hip, flank, shoulder, and/or upper arm.

Subjects who completed study SP709, were compliant, and did not have a severe application site reaction, were eligible. Subjects with a <+50% overall change in IRLS total score during SP709 were immediately enrolled in SP710. Subjects with a≥+50% overall change in IRLS

[7] Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. Measuring functioning and well-being: The Medical Outcomes Study approach. Durham, NC: Duke University Press; 1992. pp.235-59.

total score were enrolled in SP710, 7 days after their final SP709 visit if their severity of RLS worsened and they did not receive drug treatment for the RLS during this period when off treatment. Exclusion criteria were similar to those in studies SP790 and SP792. Subjects were also excluded if they had a treatment related serious adverse event (SAE) during SP709.

Efficacy endpoints

The primary variables were long-term safety and tolerability as measured by the following: collection and assessment of adverse effects (AEs); changes in haematology, blood chemistry, and urine analysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital signs (that is, blood pressure [BP], pulse rate) including an assessment of orthostatic hypotension; changes in physical and neurological examination findings; changes in Epworth Sleepiness Scale (ESS); change in Augmentation Severity Rating Scale (ASRS) total score; Global rating of tolerability by the investigator (CGI Item 4); and Global rating of tolerability by the subject (5-point scale). Efficacy measurements included change in IRLS sum score, change in Restless Legs Syndrome-6 (RLS-6) Rating Scales, change in CGI items, Responder Remitter criteria, and change in Global Subject Rating of Efficacy.

Patient disposition, baseline characteristics, compliance

A total of 295 subjects entered the trial from SP709, the preceding double-blind Phase IIb trial. Five subjects prematurely discontinued from the trial during the titration period; 4 due to AEs and 1 subject withdrew consent, resulting in 290 subjects entering the maintenance period. Of these 295 subjects, 136 (46%) subjects prematurely discontinued from the trial resulting in a total of 159 (54%) subjects completing year 3 of the maintenance period. The most common reason for premature discontinuation was adverse events (78 subjects, 26% of total), followed by lack of efficacy (24 subjects, 8% of total).

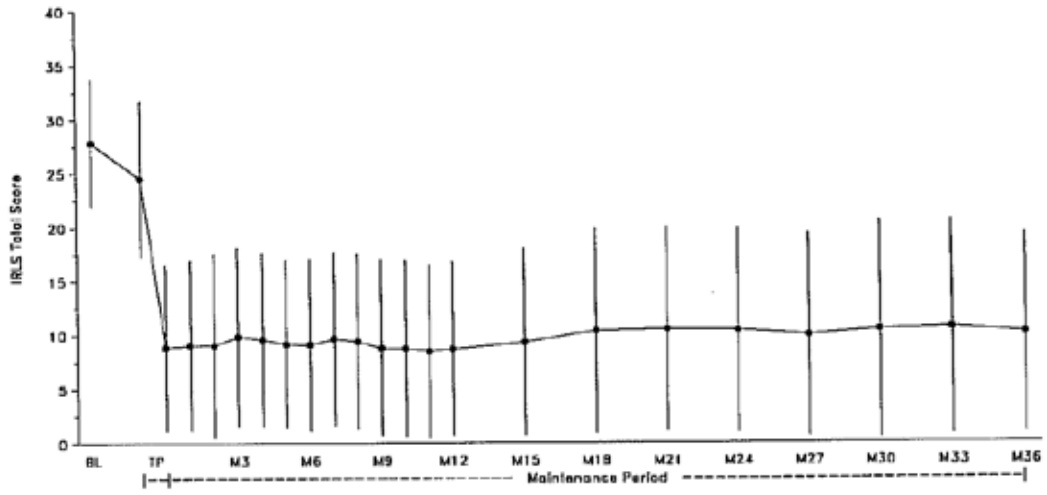
The average subject age was 58.3 years (range 22-75 years), 71% were <65 years old and 66% were female. All subjects were Caucasian. By Year 3, 31 subjects (11%) were taking a concomitant medication for RLS.

By the end of Year 2, there were major protocol deviations in 42% of subjects, the most common being taking forbidden medications (20%) followed by compliance violations (14%). Protocol deviations were not assessed in Year 3. Treatment compliance was high during the maintenance period (94%, 95% and 95% in year 1, 2 and 3 respectively). A total of 295 subjects are included in the Safety Set (SS) and the Full Analysis Set (FAS). The FAS included all subjects who had a valid baseline in SP709 and at least 1 value for efficacy during SP710.

Results

The mean decrease in IRLS sum score is presented graphically in Figure 8. This shows a maintained reduction in IRLS score from the start of the maintenance period through to the end of year 3 with a mean reduction of 17.6 points from baseline. At the end of Year 3, 51 of 159 (32%) subjects had an IRLS total score of 0 (that is, severity of “none”) and 107 (67%) were classed as Responders (IRLS score improvement from baseline of≥50%). Response was also noted on the mean CGI-Item 1 score which ranged between 2.0 and 2.3 points during the maintenance period, and the mean decrease from baseline ranged between 2.7 and 3.0 points.

Figure 8: Time response plot for mean IRLS total score through SP710 year 3 of maintenance period



BL=Baseline; FAS=Full Analysis Set; IRLS=International Restless Legs Study Group Rating Scale; TP=Titration Period; MP=Maintenance Period

The mean daily dosage of rotigotine increased slightly during 3 years of open-label treatment, ranging from 5.48 mg/day (equivalent to 2.44 mg/24 h) at the start of the maintenance period to 6.60 mg/day (equivalent to 2.93 mg/24 h) at Month 24, and to 6.74 mg/day (equivalent to 3.00 mg/24 h) at Month 36 of the maintenance period. During this time no dose adjustments were necessary in 42% (121/290), the dose was increased in 48% (138/290) and the dose was decreased in 11% (31/290) of subjects. The main reason for dose increase was lack of efficacy (127/290, 44%) and for dose decrease was an adverse event (19/290, 7%) The most frequent rotigotine dose during the 3 year maintenance period was 9 mg, 6.75 mg, 4.5 mg, 2.25 mg and 1.125 mg/day in 40%, 22%, 23%, 10% and 5% of subjects respectively**.** It seems that there was a shift to moving patients up to a higher dose – 27% started on 9 mg and 47% had it as their final dose in the maintenance period. There was a trend to increase dose and then drop out with side effects as 46% of subjects had dropped out of the study by the end of year 3 (26% due to AEs). It is interesting to note that the majority of the patients in this 3 year study were treated with the 9 mg/day patch which is higher than the maximum proposed dose of 6.75 mg/day.

SP791

Study design and patient population

This was a one year multi-centre, open-label extension trial to assess safety and tolerability of rotigotine in subjects with idiopathic RLS who previously participated in SP790 (6-month Phase III trial) or SP794 (sleep laboratory trial). This trial was conducted between January 2006 and September 2007 at 44 sites in 7 European countries. The design included an initial titration period of up to 21 days where subjects were up-titrated to their optimal dose, then a 1-year maintenance period, followed by a taper period of up to 4 days for safe, gradual withdrawal from trial medication, and a 30-day safety follow-up period.

Subjects were up-titrated weekly as required from 2.25 mg, to 4.5 mg to a maximum of 6.75 mg/day. Optimal dose was decided as per study SP710 by the investigator as the absence or

maximal reduction in RLS symptoms without intolerable side effects. Single patches were used and applied daily as per SP710.

Subjects who successfully completed the maintenance periods and the taper periods of SP790 or SP794 were eligible. Exclusion criteria included an ongoing treatment-related SAE, pregnancy or absence of contraception if pre-menopausal, and any medical or psychiatric condition that could interfere with trial participation.

Patient disposition, baseline characteristics and compliance

There were 341 subjects enrolled in the trial - 284 subjects enrolled after completion of SP790 (91% of all subjects who completed SP790) and 57 subjects enrolled after completion of SP794 (93% of all subjects who completed SP794). A total of 91 subjects (27%) prematurely discontinued from the trial. The most common reasons for premature discontinuation were adverse events (58 out of 341 subjects, 17%) and lack of efficacy (17 out of 341 subjects, 5%).

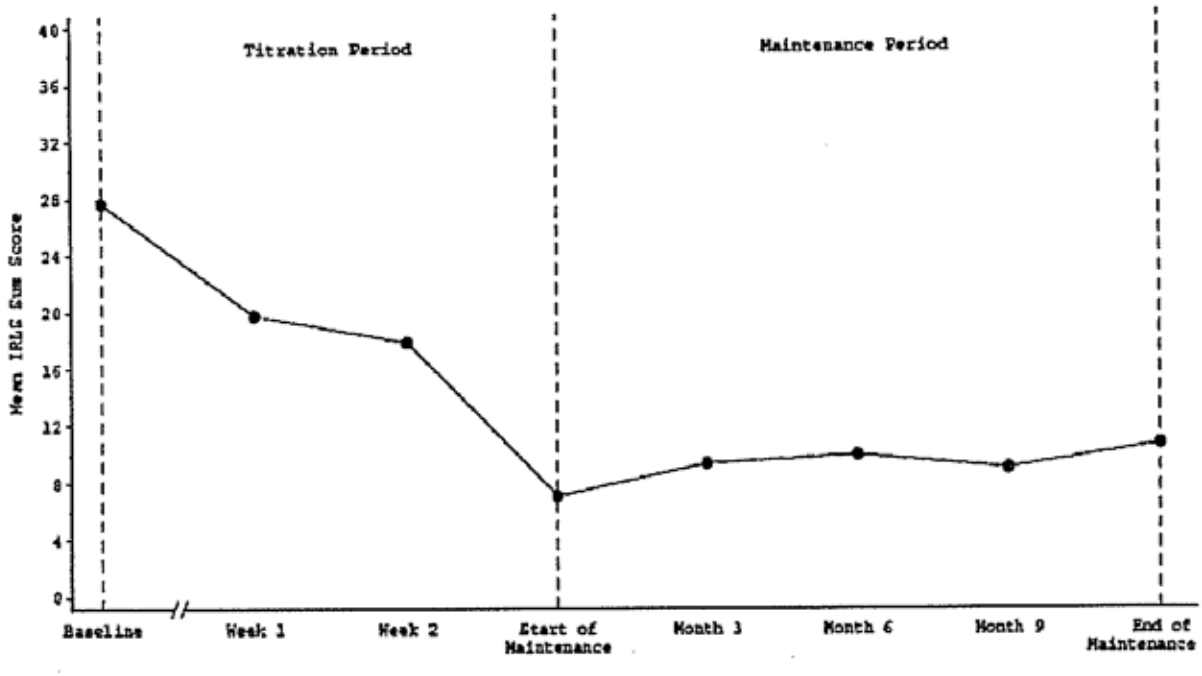
The average age of subjects was 59 (range 24-79) years with 65% being aged <65 years, 72% being females and all were Caucasian. There were no clinically relevant differences in subjects enrolling from either trial in baseline RLS disease severity. Dose exposure showed the maximum dose received during the maintenance period was 2.25 mg/day for 10% of subjects, 4.5 mg/day for 45% of subjects, and 6.75 mg/day for 44% of subjects. Protocol deviations were not analysed in this open label study though it was noted that all subjects met the eligibility criteria. The majority of subjects (97%) in the FAS were considered compliant.

Results

The mean change in the IRLS sum score from baseline of the previous trial to the end of the maintenance period of the open label trial was -17.0 with the effect maintained over the study year (Figure 9). At the end of the maintenance period, 30% had no RLS symptoms and 24% had mild RLS symptoms; however moderate symptoms were present in 28% of subjects and severe or very severe RLS symptoms were present in 17% of subjects. There were 223 of 341 (65%) subjects who were classified as IRLS responders (decrease of ≥50% in IRLS sum score from baseline to end of maintenance period) at the end of the maintenance period.

A 2.7 reduction in mean change from baseline of end of maintenance period was noted for the CGI-Item 1 (Severity of Illness) score and a shift to a less illness severe category was found in 81% of subjects. Other supportive evidence of efficacy was provided by results in CGI-Item 2 Change in Condition (69% “very much improved”), CGI-Item 3 Therapeutic Effect (very good 70%), and RLS-6 rating scales where improvements were noted in each of the subscales.

Figure 9: Time response plot for mean IRLS total score



Note: End of Maintenance includes valid assessments from subjects who dropped out and performed early withdrawal visit.
Note: Baseline = Baseline of SP790 (7 month before week 1) and of SP794 (2 month before week 1)

SP793

Study design and patient population

SP793 was a one year multi-centre, open-label extension trial in subjects who previously participated in SP792 (6-month Phase III trial). It was conducted at 48 USA sites from December 2005 to December 2007. As with the other open-label studies, there was an initial titration period of up to 28 days, a 1 year maintenance period and a 4 day taper period and a 30 day safety follow up period. Rotigotine dose was escalated in weekly increments from 1.125 mg to 2.25 mg, to 4.5 mg to a maximum of 6.75 mg/day. Optimal dose was determined by the investigator as in the other open labels trials. Single patches were administered daily as per other trials.

Subjects were included if they had completed the maintenance and taper period of SP792. Exclusion criteria were similar to the other open label studies.

Patient disposition, baseline characteristics and compliance

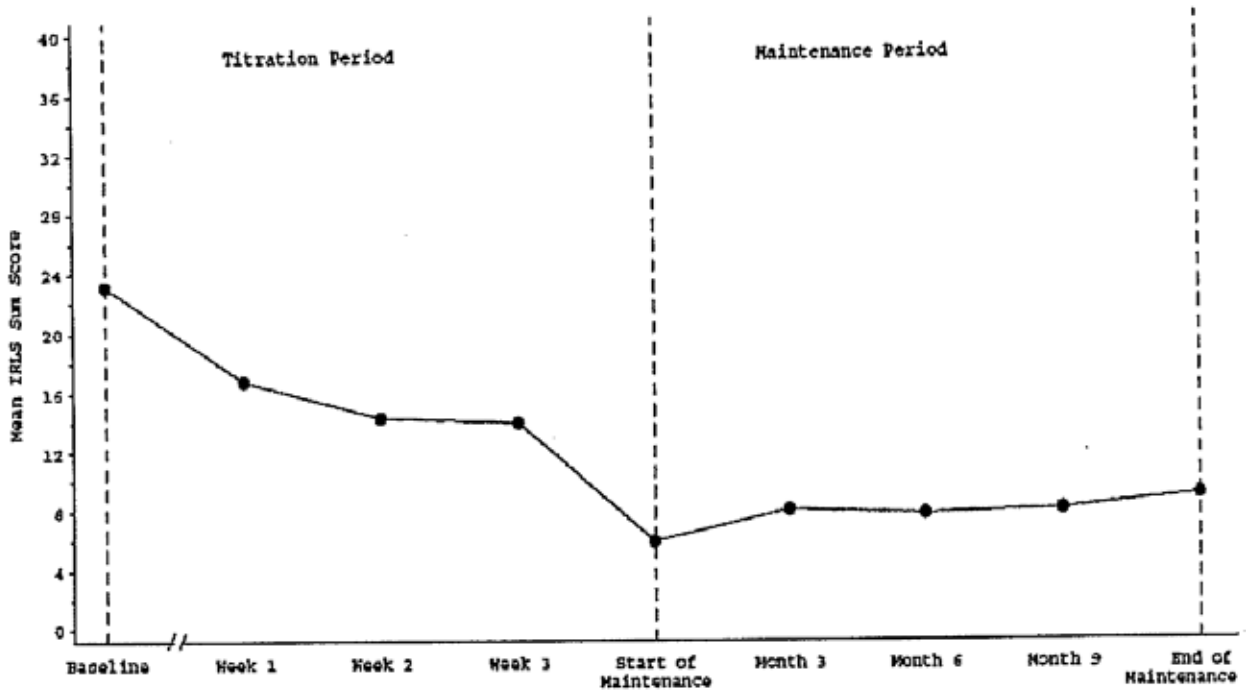
Of the 320 subjects who completed the preceding double blind trial SP792, 279 (87%) were enrolled in this trial. There were 174 (62%) subjects who completed and 105 (38%) subjects who prematurely discontinued the trial. The most common reason for discontinuation was adverse events (48%) occurring in 51 of 279 (18%) of all enrolled subjects. Other reasons for discontinuation were consent withdrawn (18%) and lack of efficacy (12%)). One subject failed eligibility criteria resulting in 278 subjects in the FAS. Protocol deviations were not analysed in this trial. Overall, 96% of subjects in the FAS were compliant with 11 subjects being non-compliant.

The average subject age was 54.2 years (range 19 to 77 years), with 80% under 65 years; 54% were female and 95% Caucasian. The mean number of years since RLS diagnosis was 2.1, and at baseline the mean IRLS sum score was 23.1. The mean daily dose at the start of the maintenance period was 3.933 mg.

Results

There was a mean reduction of IRLS sum score of 14.2 from baseline to the end of the maintenance period. The effect was maintained over the 1 year open label treatment time (Figure 10). At the end of the maintenance period, 35% of subjects reported no RLS symptoms and 28% reported mild symptoms, while 37% of subjects still had moderate, severe or very severe symptoms. At the end of the maintenance period, there was a mean reduction in the CGI-Item 1 score of 2.3, and 79% of subjects improved by this time to a less severe illness category. Consistency of the above results were supported by other efficacy results in CGI-Item 2 Change in Condition (59% "very much improved"), CGI-Item 3 Therapeutic Effect (very good 70%), and RLS-6 rating scale with improvements in each of the subscales.

Figure 10: Time response plot for mean IRLS total score



Note: End of Maintenance includes valid assessments from subjects who dropped out and performed early withdrawal visit.
Note: Baseline = Baseline of SP792 (7 month before week 1)

Summary of Efficacy

In the two pivotal phase III trials (SP790 and SP792), there were 213 subjects who received placebo and 728 who received rotigotine in the FAS. Treatment duration was 6 months plus an initial titration period of 3 to 4 weeks. Doses evaluated included 2.25 mg/day, 4.5 mg/day, and 6.75 mg/day for both studies and 1.125 mg/in one study. The subjects were adults with moderate to severe restless legs syndrome symptoms as based on a standardised rating scale.

Two co-primary efficacy endpoints were evaluated: the sum score of the patient-rated Restless Legs Syndrome Rating Scale (IRLS) and physician-rated Clinical Global Impression

(CGI) Item 1 Severity of Illness score. Both scales are internationally recognised for assessing efficacy of RLS treatments. Doses of 2.25 mg/day, 4.5 mg/day and 6.75 mg/day all showed statistically significant efficacy over placebo in reductions of these two scores after approximately 7 months of treatment. Trends suggesting dose-dependent response was also evident with greater reductions in symptoms and illness severity with higher doses. The dose of 1.125 mg/day did not demonstrate significant change compared to placebo.

Treatment response was greater in the European trial SP790 (net treatment effect of rotigotine over placebo was -5.1 to -8.2 for IRLS sum score, and -0.8 to -1.2 for CGI-Item 1) compared to the US trial SP9792 (-2.2 to -5.2 for IRLS sum score and -0.35 to -0.9 for CGI-Item 1). This may be explained by more severe disease in the SP790 subjects with baseline IRLS scores of 28 to 28.2 compared to baseline IRLS scores of 23.1 to 23.6 in study SP792.

Supportive evidence of efficacy was also provided by the 2 Phase II studies which used the IRLS sum score as the primary efficacy endpoint. In the Phase IIa trial SP666, the dose of 4.5 mg/day showed a statistically significant treatment difference to placebo. In the Phase IIb study (SP709), a dose response was evident and treatment difference between rotigotine and placebo was significant for doses of 2.25 mg, 4.5 mg, 6.75 mg and 9 mg/day, although the highest dose (9 mg/day) showed no additional benefit over the preceding dose of 6.75 mg.

A sleep laboratory study which measured period limb movements as the primary endpoint demonstrated that rotigotine was significantly more effective than placebo in the reduction of the PLMI at the end of a 7 week treatment period.

Long term efficacy data, whilst not the primary outcome, were examined from three open label long term safety studies involving 955 patients. Symptom reduction was maintained after an additional one year (SP791 and SP793) and 3 years (SP710) of treatment. Increases in rotigotine dose during three years of open label treatment were modest.

A greater treatment effect was seen in females, in those with more severe disease at study onset, and in those who had been previously treated with other RLS therapies. Age, tobacco use and alcohol use did not alter treatment effect.

Safety

Safety Overview

A total of 1432 subjects with RLS (1309 subjects treated with rotigotine) were evaluated for safety. Subjects who have received at least 1 dose of study medication were included in the safety analyses. The sponsor's *Summary of Clinical Safety* used a cut-off date of 31 January 2007 for data inclusion from the ongoing open label trials. Safety data in subjects with RLS were analysed in the following 4 data pools:

- Primary safety pool, Pool RS1. The two Phase III pivotal trials (SP790 and SP792) containing 962 subjects (745 subjects randomized to rotigotine and 217 subjects randomized to placebo).
- Open-label safety pool, Pool RS2. The three open-label trials (SP710, SP791, and SP793) containing 914 subjects treated with rotigotine.
- Other safety pools, Pool RS3. All Phase II or III trial rotigotine-treated subjects (randomised or open label) (SP666, SP709, SP790, SP792, SP794, SP710, SP791, and SP793). This pool contains 1309 subjects.
- Other safety pools, Pool RS4. All Phase II or III subjects with RLS (not including open-label extension data or trial SP794): trials SP666, SP709, SP790, and SP792. This pool

contains 1365 subjects (1079 subjects randomized to rotigotine and 286 subjects randomized to placebo).

Safety Data Collection

Adverse events were captured during clinic visit by direct questioning, physical (including neurological) examination including vital signs, laboratory evaluations and ECGs. There was central reading of ECGs and a central laboratory. In addition, at specified visits subjects completed scales for daytime sleepiness, sleep characteristics, and depression. The investigators scored the CGI-Item 4 (side effects), augmentation severity rating, and assessed patch application site and patch adhesiveness.

Duration of exposure

For the primary pool (RS1) 748 subjects were exposed to rotigotine for an average of approximately 6 months (mean treatment duration was 167.2 days, SD 69.5). The mean daily dose was 1.5 mg/24 hours. In the open label trials (pool RS2), 914 subjects were exposed to rotigotine for an average of about 1 year (mean treatment duration 418.1 days, SD 368.5). The mean daily dose was 2.2 mg/24 h and the dose that was taken for the longest duration during open label treatment was 1 mg in 19%, 2 mg in 33% and 3 mg/24 h in 28% of subjects. For all rotigotine-treated subjects (pool RS3), there were 1309 subjects with 1433 subject-years of exposure, including 192 (14.7%) subjects treated for over 24 months. The rotigotine dose that was taken for the longest duration was 2 mg (29% of subjects) followed by 1 mg (25%) and 3 mg/24 h (23%). In the higher rotigotine dose group of 3 mg/24 h, exposures were 6 to 12 months for 83 subjects (28%), 1 to 2 years for 112 subjects (38%), and >2 years for 34 subjects (11%).

Safety in Pivotal Studies

Adverse Events

In the primary safety Pool RS1 (two phase III pivotal trials), 68% of placebo-treated subjects and 83% of all rotigotine-treated subjects with RLS had at least 1 treatment-emergent adverse event (TEAE) (Table 13). The AEs with the highest incidence in rotigotine-treated subjects were “application and instillation site reactions” (34% vs 4% placebo), nausea (19% vs 10%), headache (17% vs 11%) and asthenic conditions/fatigue (11% vs 8%). Other TEAEs that were more common in rotigotine-treated subjects compared to placebo included: non-application site skin reactions (10% vs 6%); increased sweating (4% vs 2%); disturbances in initiating and maintaining sleep (5% vs 3%); somnolence (8% vs 4%); vomiting (3% vs 1%), dyspepsia (2% vs 1%), and hypertension (2% vs 0). Similar overall incidences were observed in the rotigotine and placebo groups for dizziness (7% vs 6%); oedema (2% each); eye disorders (<1% each); gynaecomastia (<1% vs 0%); hallucination (<1% each); and weight gain (1% each).

Table 13: Safety in Pivotal Phase III Studies SP790 and SP792

Treatment-emergent adverse events occurring in at least 5% of all rotigotine-treated subjects by randomized dose (Pool RS1)

MedDRA SOC/ HLT[a] or PT	Placebo N=217 n (%)	Rotigotine dose				
		0.5mg/24h N=99 n (%)	1mg/24h N=215 n (%)	2mg/24h N=211 n (%)	3mg/24h N=220 n (%)	Total N=745 n (%)
At least 1 AE	148 (68.2)	83 (83.8)	172 (80.0)	179 (84.8)	185 (84.1)	619 (83.1)
Gastrointestinal disorders						
Nausea	21 (9.7)	18 (8.2)	32 (14.9)	48 (22.7)	45 (20.5)	143 (19.2)
General disorders and administration site conditions						
Application and instillation site reactions[a]	8 (3.7)	23 (23.2)	57 (26.5)	80 (37.9)	95 (43.2)	255 (34.2)
Application site erythema	4 (1.8)	7 (7.1)	32 (14.9)	30 (14.2)	40 (18.2)	109 (14.6)
Application site pruritus	0	7 (7.1)	20 (9.3)	37 (17.5)	36 (16.4)	100 (13.4)
Application site reaction	4 (1.8)	4 (4.0)	12 (5.6)	17 (8.1)	30 (13.6)	63 (8.5)
Asthenic conditions[a]	18 (8.3)	11 (11.1)	16 (7.4)	30 (14.2)	26 (11.8)	83 (11.1)
Fatigue	17 (7.8)	11 (11.1)	15 (7.0)	28 (13.3)	24 (10.9)	78 (10.5)
Infections and infestations						
Nasopharyngitis	15 (6.9)	5 (5.1)	22 (10.2)	15 (7.1)	17 (7.7)	59 (7.9)
Upper respiratory tract infection	13 (6.0)	6 (6.1)	10 (4.7)	10 (4.7)	12 (5.5)	38 (5.1)
Nervous system disorders						
Headache	24 (11.1)	21 (21.2)	33 (15.3)	37 (17.5)	34 (15.5)	125 (16.8)
Somnolence	9 (4.1)	8 (8.1)	10 (4.7)	16 (7.6)	22 (10.0)	56 (7.5)
Dizziness	12 (5.5)	7 (7.1)	10 (4.7)	18 (8.5)	14 (6.4)	49 (6.6)
Psychiatric disorders						
Disturbances in initiating and maintaining sleep[a]	7 (3.2)	2 (2.0)	9 (4.2)	7 (3.3)	21 (9.5)	39 (5.2)
Skin and subcutaneous tissue disorders						
Pruritus	7 (3.2)	9 (9.1)	9 (4.2)	7 (3.3)	15 (6.8)	40 (5.4)

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

a The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions, disturbances in initiating and maintaining sleep, and perception disturbances.

Note: This table presents PTs and selected HLTs occurring in at least 5% of rotigotine-treated subjects; corresponding SOCs are reported for completeness.

In rotigotine-treated subjects, dose-related trends were observed for the percentage of subjects with application and instillation site reactions, nausea, somnolence, and disturbances in initiating and maintaining sleep (Table 14). All occurrences of application site reactions and most occurrences of nausea, fatigue, somnolence, and dizziness were regarded as related to the trial medication by the investigators.

Table 14: Safety in Pivotal Phase III Studies SP790 and SP792

Treatment-emergent adverse events showing dose-related trends in the randomized analysis by dose of longest duration (Pool RS1)

MedDRA SOC/ HLT[a] or PT	Placebo N=214 N (%)	Rotigotine dose 0.5mg/24h N=139 n (%)	1mg/24h N=259 n (%)	2mg/24h N=183 n (%)	3mg/24h N=167 n (%)	Total N=748 n (%)
Gastrointestinal disorders						
Nausea	20 (9.3)	27 (19.4)	46 (17.8)	43 (23.5)	28 (16.8)	144 (19.3)
General disorders and administration site conditions						
Application and instillation site reactions[a]	7 (3.3)	30 (21.6)	72 (27.8)	74 (40.4)	80 (47.9)	256 (34.2)
Nervous system disorders						
Somnolence	9 (4.2)	15 (10.8)	13 (5.0)	17 (9.3)	11 (6.6)	56 (7.5)
Psychiatric disorders						
Disturbances in initiating and maintaining sleep[a]	7 (3.3)	3 (2.2)	12 (4.6)	5 (2.7)	19 (11.4)	39 (5.2)

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

a The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions, disturbances in initiating and maintaining sleep, and perception disturbances.

Note: Selection based on criteria outlined in Section 2.7.4.2.1.1 for the randomized analysis. This table includes PTs and selected HLTs; corresponding SOCs are reported for completeness.

Severe intensity TEAEs occurred in 17.4% of rotigotine-treated subjects compared to 9.7% of placebo-treated subjects. In rotigotine-treated subjects, the percentage of subjects who experienced at least 1 severe TEAE was 14% in the 2 lower dose groups and 20% in the 2 higher dose groups. The severe TEAEs in rotigotine-treated subjects were nausea (1.5%), application site reaction (2.8%), headache (1.3%), and sleep disturbance (1.3%) (Table 15).

Table 15: Safety in Pivotal Phase III Studies SP790 and SP792

Severe, treatment-emergent adverse events occurring in at least 1% of rotigotine-treated subjects by randomized dose (Pool RS1)

MedDRA SOC/ HLT[a] or PT	Placebo N=217 n (%)	Rotigotine dose 0.5mg/24h N=99 n (%)	1mg/24h N=215 n (%)	2mg/24h N=211 n (%)	3mg/24h N=220 n (%)	Total N=745 n (%)
At least 1 severe AE	21 (9.7)	14 (14.1)	30 (14.0)	42 (19.9)	44 (20.0)	130 (17.4)
Gastrointestinal disorders						
Nausea	1 (0.5)	0	1 (0.5)	6 (2.8)	4 (1.8)	11 (1.5)
General disorders and administration site conditions						
Application and instillation site reactions[a]	0	1 (1.0)	4 (1.9)	6 (2.8)	10 (4.5)	21 (2.8)
Application site reaction	0	0	1 (0.5)	3 (1.4)	7 (3.2)	11 (1.5)
Nervous system disorders						
Headache	0	2 (2.0)	2 (0.9)	4 (1.9)	2 (0.9)	10 (1.3)
Psychiatric disorders						
Disturbances in initiating and maintaining sleep[a]	2 (0.9)	1 (1.0)	4 (1.9)	2 (0.9)	3 (1.4)	10 (1.3)
Insomnia	2 (0.9)	1 (1.0)	4 (1.9)	1 (0.5)	3 (1.4)	9 (1.2)

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

Among rotigotine-treated subjects, the incidence of nausea was higher during the titration period with the median time to first onset of nausea being 8 days. The incidence of application and instillation site reactions was higher in the maintenance and the median time to first onset was 58 days.

Deaths, SAEs, discontinuations and dose reductions due to AEs

Deaths

At the cut-off of 31 Jan 2007, there had been one death among subjects participating in the RLS clinical trial program. A 66 year old female died following aortic valve replacement surgery for aortic stenosis and ventricular hypertrophy, she had been exposed to rotigotine for 184 days (trial SP794 and SP791) at a maintenance dose of 2 mg/24 h. Whilst the death was considered as unlikely to be related to the trial medication by the investigator, the diagnosis of the valvular disease occurred after 57 days of exposure to rotigotine.

A second death occurred in a 73 year old man after the safety cut-off (June 2007). The subject had been exposed to rotigotine for 366 days at a maintenance dose of 4.5 mg/day (trials SP790 and SP791). He had a history of ischaemic heart disease and hypertension and died following a myocardial infarction which was not considered related to the trial medication by the investigator.

SAEs

In the primary safety pool (RS1) the incidence of SAEs was similar in the placebo group (4%, 9/217) and rotigotine group (6%, 42/745). For rotigotine-treated subjects, the overall incidence of SAEs was 3%, 6%, 5%, and 7% in the 0.5 mg/24 h, 1 mg/24 h, 2 mg/24 h, and 3 mg/24 h randomized dose groups, respectively. The most frequent SAEs were application and instillation site reactions (n=6, 1% of all rotigotine-treated subjects), cholecystitis (n=2, 0.3%), pneumonia (n=2, 0.3%) and syncope (n=2, 0.3%).

Discontinuations due to AEs

In Pool RS1, 6% of placebo-treated subjects and 18% of all rotigotine-treated subjects with RLS had a TEAE that led to discontinuation of trial medication. Among rotigotine-treated subjects, the overall incidence of discontinuation of trial medication due to a TEAE was 9%, 16%, 18%, and 25% in the 0.5 mg/24 h, 1 mg/24 h, 2 mg/24 h, and 3 mg/24 h randomized dose groups, respectively. The most common reasons were application and instillation site reactions (7%), nausea (1%), dizziness (1%) and fatigue (1%). There was an apparent dose-related effect for trial discontinuation due to application site reactions with increasing incidence with increasing dose.

Dose reductions due to AEs

In Pool RS1, more rotigotine-treated subjects had a TEAE leading to dose reduction compared to placebo-treated subjects (8% versus 1%). Those occurring in ≥1% of subjects were nausea (n=14, 2% total rotigotine vs n=0 placebo); somnolence (n=11, 2% vs n=1, 1%); fatigue (n=10, 1% vs n=2, 1%); and headache (n=8, 1% vs n=0).

Specific adverse events of interest

In the primary safety pool (RS1), similar overall incidences were observed in the rotigotine and placebo groups for the following TEAEs of special interest: cardiac arrhythmias (4% total rotigotine vs 3% placebo); events suggestive of falls (5% vs 6%); events suggestive of fibrosis (<1% vs 0%); severe hypotension and orthostatic hypotension (0% each); syncope (1% vs <1%); and valvulopathy (<1% vs 0%).

Higher incidences were observed in the rotigotine group compared with placebo for compulsive behaviour (3% vs 1%), sleep attacks (2% vs 1%), and reproductive and breast disorders (7% vs 4%). For compulsive behaviour most common preferred terms were libido increased (14 subjects), libido disorder (4 subjects), and erection increased (3 subjects). For reproductive and breast disorders in the rotigotine group the most common AEs were menstrual disorder (8 subjects), erectile dysfunction (6 subjects), and menorrhagia (4 subjects).

Laboratory investigations and vital signs

Haematology

There were no significant changes in haematology parameters in the rotigotine group compared to the placebo group. In Pool RS1, markedly abnormal haematology values at any time during treatment were found in 10/217 (5%) subjects randomised to placebo and 33/745 (4%) subjects randomised to rotigotine. The only TEAEs from haematology investigations reported by >1 subject in the total rotigotine group were serum ferritin decreased (rotigotine vs placebo: 2% vs <1%), blood iron decreased (<1% vs 1%), anaemia and leukopenia (<1% vs 0%).

Chemistry and endocrine

In Pool RS1, one or more markedly abnormal chemistry value at any time during treatment was noted in 60% (130/217) of placebo-treated subjects and 63% (472/745) rotigotine-treated subjects. No subjects had a combination of markedly abnormal high ALT and total bilirubin or AST and total bilirubin. The frequency of TEAEs related to chemistry in the rotigotine-treated subjects was similar to or lower than that in placebo-treated subjects.

A shift to a low value of prolactin during treatment was noted in 10% of the total rotigotine group compared to 4% of the placebo group. There was a higher incidence of low prolactin level with increasing rotigotine dose.

Urinalysis

In Pool RS1, treatment-emergent AEs related to urinalysis findings reported by >1 subject were <1% in both the rotigotine and placebo groups.

Vital Signs

In pool RS1, mean changes in weight from baseline were similar between rotigotine and placebo groups. The mean changes from baseline for systolic blood pressure, diastolic blood pressure, and pulse rate were small, and were not considered to be clinically relevant. Systolic and diastolic blood pressure abnormalities at final visit were generally comparable between the placebo and rotigotine groups. There was a dose related increase in new orthostatic hypotension with respect to pulse rate increase ≥15 beats per minute in the rotigotine group from 28% in the 0.5 mg/24 h group to 42% in the 3 mg/24 h group. The incidence of severe orthostatic hypotension (systolic blood pressure decrease≥40 mmHg or diastolic blood pressure decrease ≥20 mmHg) was the same in placebo and rotigotine groups (7% each). Related TEAEs reported by ≥1% of subjects were dizziness (6% of the total rotigotine group and 6% of the placebo group), vertigo (1% and 1%), and syncope (1% and <1%).

ECGs

The "Thorough QT/QTc trial" (SP864) demonstrated that rotigotine did not prolong the QTc interval in male and female subjects with PD following therapeutic and supratherapeutic doses up to 24 mg/24 h.

In pool RS1, there was no evident difference between placebo and rotigotine treatment for PR interval, QRS duration, or prolongation of the QTc interval.

Safety in Specific Subgroups

Race

The small number of non-White subjects (25 compared to 723 White subjects) precludes any meaningful comparison of rotigotine exposure by ethnicity from these RLS trials.

Age

A trial inclusion criterion was 18 to 75 years, so data on those aged over 75 year is not available. In Pool RS1, adverse event reporting was similar in subjects <65 years (84%) to those aged ≥65 years (81%). The only TEAE reported at a rate >5% higher in one age subgroup compared to the other was nausea (21% of subjects aged <65 years and 15% of subjects ≥65 years of age). SAEs were more frequent in the elderly (4% of subjects aged <65 years and 11% of subjects ≥65 years), however the only SAEs reported at a rate >1% different in one age subgroup compared to the other were "application and instillation site reactions" with this being more frequent in those aged ≥65 years (2%) compared to the younger group (<1%).

Gender

TEAEs were reported in 84% of females and 82% of males. Nausea and application site reactions were more frequent in females (22% and 38% respectively) compared to males (14% and 26%). TEAEs leading to discontinuation occurred in 20% of females and 14% males. SAEs were reported by 5% of females and 7% of males and no SAEs were reported at a rate of >1% different in either gender.

Concomitant disease

For rotigotine-treated subjects with a concomitant disease (as reported on the medical history for >10% of subjects in Pool RS1), there were no TEAEs occurring at >10% higher rate, or SAEs occurring at >2% higher rate, compared to those without the disease.

Pregnancy

There were no reported pregnancies at the time of data cut-off (31 Jan 2007) for the safety analysis. However information on 3 pregnancies was located within individual study reports.

1. A 23 year old female has a positive pregnancy test during the Maintenance period (SP792) after 207 days of treatment at a dose of 1.125 mg/day. She was withdrawn from the study. The outcome of the pregnancy was not reported.
2. A 21 year old female was noted to be pregnant after 225 days of treatment with rotigotine (randomised and open label SP793). Treatment was ceased and the subject delivered a healthy baby girl at 35 weeks gestation. No AEs were reported for the baby.
3. A 30 year old female had a positive pregnancy test at her termination visit (after 624 days of randomised and open label SP710treatment). She had a planned termination of pregnancy.

Withdrawal, rebound and augmentation

For studies included in Pool RS1, subjects who prematurely discontinued the trial or who declined to enrol in the open-label portion of the trial had a safety follow-up visit 30 days after beginning de-escalation at which time AEs were assessed. During this safety follow-up

period, 11/108 (10%) of placebo-treated subjects reported 17 TEAEs and 36/332 (11%) of rotigotine-treated subjects reported 51 TEAEs. There were no evident patterns in these AEs.

Augmentation, or worsening of RLS symptoms during treatment, was assessed using a specific scale (Augmentation Severity Rating Scales – ASRS) with scores from 1 to 4. A score of >1 is considered possible augmentation. At the end of 6 months of treatment ASRS scores of >1 were similar between rotigotine groups (5%) and placebo groups (6%). For rotigotine subjects withdrawing early (n=180), the mean ASRS score was 0.324 (SD=0.451) which was slightly lower than the mean score for the placebo group (0.452, SD=0.508, n=63).

Rebound is an end of dose effect and was evaluated as an increase of RLS symptoms beyond baseline severity after treatment cessation. A limited analysis was conducted in 43 subjects (33 on rotigotine and 10 on placebo) who had mean drug free period of 6 days between randomised (SP709) and open label trials (SP710). The mean change in the IRLS sum score from baseline to the end of the drug free period in the rotigotine subjects was 1.0 (SD=6.1) which did not suggest a worsening of symptoms.

Long term evidence of safety

Long term safety has been evaluated in the three open label trials, two (SP791 and SP793) of which ran for 1 year and the third (SP710) has data available from the end of Year 3. The open label pooled safety data is captured in Pool RS2 up to the cut off of 31 January 2007, despite these trials being ongoing.

In Pool RS2, 914 subjects were exposed to rotigotine, with a maximum duration of exposure of 1272 days (~3.5 years). A total of 466 subjects (51%) received rotigotine for 6 to 12 months, while 190 subjects (21%) received rotigotine for 24 months or longer. The majority of subjects were exposed to mean rotigotine doses ranging from 1 to <2 (37%) or 2 to <3 mg/24 h (35%) followed by 0.5 to <1 (14%) and 3 to <4 mg/24 h (14%).

There were 77% of subjects in Pool RS2 who experienced at least 1 TEAE, the highest incidence were “application and instillation site reactions” (34%) and nausea (10%). Severe intensity TEAEs occurred in 16% (150/914) of subjects with the most being “application and instillation site reactions” (53/914, 6%) and fatigue (7/914, 1%). The only TEAE with a rate of at least 1 event per 100 person-months was application and instillation site reaction (4.322).

In addition, 4/914 (<1%) subjects experienced treatment-emergent compulsive behaviour, 9/914 (1%) experienced sleep attack/sudden onset of sleep, 14/914 (2%) subjects experienced syncope and 2/914 (<1%) subjects had treatment-emergent valvulopathy. These were the death discussed previously in a subject with aortic stenosis and a second case with aortic valve incompetence on a dose of 4 mg/24 h. There were also 10/914 (1%) subjects who experienced an endocrine disorder including hypothyroidism (6 subjects), goitre (3 subjects), and hyperthyroidism (1 subject). Endocrine TEAEs were also captured by investigations and included decreased blood testosterone (4 subjects) and increased blood prolactin (2 subjects).

In Pool RS2, 19% (170/914) of rotigotine-treated subjects had a TEAE leading to discontinuation of the trial medication, the most common reasons being application site reactions (11%) and nausea (1%).

In Pool RS2, 10% of all rotigotine-treated subjects with RLS had at least 1 SAE. There was a dose-related increase in SAE incidence (6%, 4%, 10%, 11%, and 19% of subjects who received 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg/24 h of rotigotine respectively). No specific SAE was reported in >1% of all rotigotine-treated subjects, the most frequent SAEs were

osteoarthritis (n=8, 1%), uterine leiomyoma (n=4, <1%), and syncope (n=3, <1%). In the safety pool RS3 (all phase 2 and 3 rotigotine subjects, randomised and open label), of the 1309 subjects there were 20 (2%) with an SAE assessed by the investigator as drug-related. The most frequent were application and instillation site reactions (n=6, <1%), nausea (n=2, <1%), syncope (n=2, <1%), and sleep attacks (n=2, <1%) (Table 16).

Table 16: All drug-related serious adverse events occurring in rotigotine-treated subjects (Pool RS3)

MedDRA SOC/ HLT[b] or PT	Total Rotigotine N=1309 n (%)
At least 1 drug-related SAE	20 (1.5)
Cardiac Disorders	
Sinus bradycardia	1 (<0.1)
Ear and labyrinth disorders	
Tinnitus	1 (<0.1)
Gastrointestinal disorders	
Nausea	2 (0.2)
General disorders and administration site conditions	
Application and instillation site reactions[a]	6 (0.5)
Application site reaction	6 (0.5)
No therapeutic response	1 (<0.1)
Injury, poisoning and procedural complications	
Fall	1 (<0.1)
Investigations	
Electrocardiogram change	1 (<0.1)
Hepatic enzyme increased	1 (<0.1)
Nervous system disorders	
Syncope	2 (0.2)
Balance disorder	1 (<0.1)
Somnolence	1 (<0.1)
Memory impairment	1 (<0.1)
Dizziness	1 (<0.1)
Dysarthria	1 (<0.1)
Psychiatric disorders	
Sleep attacks	2 (0.2)
Confusional state	1 (<0.1)
Vascular disorders	
Deep vein thrombosis	1 (<0.1)

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

a The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions, disturbances in initiating and maintaining sleep, and perception disturbances.

Safety in supportive studies and in healthy volunteers

There were no additional safety findings of note from the Phase IIa study (SP666), Phase IIb study (SP709), or Phase III sleep study (SP794), nor from the Thorough QT trial (SP864).

Summary of safety

As similar safety results were seen on the two Phase III randomised controlled trials (SP790 and SP792) safety was assessed from the primary safety database of pooled data. This contained data from 748 subjects treated with rotigotine for a mean duration of about 6 months (167 days). This was supplemented by data from 3 open label extension studies with 914 subjects treated for about 1 year (mean 418 days). The database cut-off was 31 January 2007. These databases are sufficient in terms of patient numbers and treatment duration to undertake a primary safety assessment.

Compared to placebo, the incidence of AEs (rotigotine vs placebo: 83% vs 68%), SAEs (6% vs 4%) and discontinuations due to AEs (18% vs 6%) were more frequent in rotigotine-treated subjects. The transdermal patch delivery system was the most frequent cause of AEs (34% of rotigotine-treated subjects vs 4% in placebo). In addition, 1% of all rotigotine-treated

subjects had the reaction severe enough to be classed as an SAE (the most frequent cause of an SAE). As with other dopamine agonists, frequent AEs were nausea (19%), headache (17%), fatigue (11%), somnolence (8%), dizziness (7%) and sleep disorders (5%). Such AEs also showed dose-related trends. Medication intolerance, particularly with increasing dose, was moderate. Eighteen per cent of all rotigotine subjects had an adverse event leading to ceasing the medication (compared to 6% of placebo subjects). Again the main reasons for stopping medication were patch site reactions, nausea, dizziness and fatigue.

Specific adverse events that occurred more frequently in those taking rotigotine were compulsive behaviour (3% vs<1%), sleep attacks (2% vs <1%), syncope (1% vs <1%) and valvulopathy (<1% vs 0%). There was no greater incidence of orthostatic hypotension, falls, arrhythmias or fibrosis. There were 2 cases of valvulopathy (aortic stenosis and incompetence). The subject with aortic stenosis was diagnosed after 57 days of rotigotine exposure and died post surgery.

Haematology and clinical chemistry and urinalysis investigations were not remarkable. As is seen with dopamine agonists, prolactin levels were seen to decrease. Whilst there was no greater incidence of severe orthostatic hypotension, 1% of rotigotine subjects had an AE of syncope compared to <1% of placebo subjects. ECG findings were unremarkable and a thorough QT trial in PD patients did not show any evidence of QTc prolongation at doses up to 24 mg/24 hours.

Conclusions regarding treatment in a non-Caucasian population cannot be made due to lack of such subjects in the database. Whilst there were 3 pregnancies reported no conclusions can be drawn on the effect of treatment in pregnant women. There were no specific safety issues in subgroup analysis by age, gender, or concomitant disease.

Augmentation (worsening of symptoms during treatment) was assessed at early withdrawal and after 6 months of treatment and was not more evident compared to placebo. Rebound was only assessed in a limited population (33 rotigotine subjects) and whilst it did not suggest symptom increase on treatment cessation, this population is too small to make a meaningful conclusion.

The longer term safety analysis (data for an additional 1 year of treatment) showed safety results similar to those observed following short term treatment with rotigotine.

Post-marketing Experience

The international birth date (IBD) for the rotigotine transdermal patch is 15 February 2006 which was the date of first marketing approval in the EU. There were 357 subjects with 678 spontaneous adverse events reported up to the 31 January 2007. Those AEs (non-serious and serious) that occurred in ≥5 subjects are summarised in Table 17. These events are similar to those seen in the clinical trials. There were 39 SAEs with 2 cases each of dizziness, psychotic disorder, sleep attacks, peripheral oedema.

Table 17: Spontaneous postmarketing adverse events reported by ≥5% of subjects

System Organ Class/Preferred Term	Number of AEs
Total AEs (non-serious and serious)	678
Gastrointestinal disorders	
Nausea	41
Vomiting	17
Diarrhoea	6
General disorders and administration site conditions	
Application site erythema	49
Application site pruritus	30
Fatigue	18
Application site reaction	15
Oedema peripheral	11
Drug ineffective	9
Application site vesicles	9
Application site swelling	9
Application site irritation	9
Application site hypersensitivity	8
Drug effect decreased	5
Infection and infestations	
Application site pustules	6
Injury, poisoning and procedural complications	
Fall	8
Musculoskeletal and connective tissue disorders	
Mobility decreased	7
Pain in extremity	7
Nervous system disorders	
Dizziness	22
Tremor	22
Headache	12
Somnolence	6
Hyperkinesia	6
Psychiatric disorders	
Restlessness	9
Hallucination	9
Sleep disorder	9
Confusional state	5
Hallucination, visual	5
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	5
Skin and subcutaneous tissue disorders	
Erythema	25
Pruritus	24
Skin reaction	11
Hyperhidrosis	10
Skin irritation	7
Vascular disorders	
Hypertension	5

AE=adverse event

PSUR Number 5.

Periodic Safety Update Report (PSUR) Number 5 covers the period from 16 February 2008 to 15 August 2008. Doses on the market were 2, 4, 6, and 8 mg/24 hour transdermal patches. During this reporting period crystal formation was noted in some rotigotine patches which led to a recall of the product and a change to the refrigerated storage (≤5 °C) conditions.

During the 6 month period, it was estimated that there were 7.8 million patient days of treatment (21,000 patient years), 7.67 million with marketed product and 141,000 with clinical trial product. There were 534 case reports with 1209 adverse events received; 108 were from clinical trials, 11 from post-marketing surveillance studies, and 388 were spontaneous. Of these adverse events, 848 were assessed as drug-related of which 179 were serious. Of the 361 assessed as not drug-related 295 were serious. There were 72 serious adverse drug reactions (ADRs) that were unexpected. There were 4 deaths (bone marrow aplasia, renal failure, CNS lymphoma, and Parkinson's disease worsening).

Compared to the previous reporting period the sponsor reported a similar patient exposure but a higher number of reported events. This it believes was a result of increased reporting due to the product recall.

During the reporting period the cases of interest included: 1 bone marrow aplasia, 2 myocardial infarction, 4 cases of atrial fibrillation (AF), 1 supraventricular tachycardia (SVT), 4 cases of circulatory collapse and 1 of cardiac insufficiency, 1 pancreatitis, 1 cholestatic hepatitis, 1 severe allergic reaction, 1 rhabdomyolysis and renal failure, 4 sleep attacks and 1 sudden onset sleep, 1 convulsion, 4 cases of compulsive gambling, 2 cases of hypersexuality, 3 cases of renal dysfunction, 1 case of hyperpigmentation, and 1 neuroleptic malignant syndrome.

There were 6 pregnancies reported, 5 from clinical trials (3 of which have already been commented on). For the other 3, there were 2 first trimester abortions (1 spontaneous, the other planned) and the one healthy term baby whose father was on trial medication. Three of the women who became pregnant were taking oral hormonal contraception. The woman taking Monostep reported diarrhoea and the other 2 were taking Diane 35 and Lo/Ovral. It is noted that the drug interaction study with oral hormone contraception did not show an effect of rotigotine on suppression hormone levels.

Safety information was updated to include the association with peripheral oedema in some Parkinson's patients and allergic reactions to sodium metabisulfite.

PSUR Number 6.

PSUR Number 6 covers the period from 16 August 2008 to 15 February 2009. During this period, the indications for rotigotine therapy were extended to RLS in some European countries. This included the new doses of 1 and 3 mg/24 hours. There was a recall of product in Switzerland to replace stock with that manufactured and stored under cold chain conditions due to the crystallisation issue described in PSUR No 5. Singapore did not approve the product due to the change to cold storage and lack of long term stability data.

The estimated number of patients exposed to rotigotine during the reporting period was 31,178 with 15,961 patient years of exposure, which was less than the previous reporting period (21,018 patient-years). There were 445 case reports with 145 being serious and unlisted.

New cases reported during the period included: 1 atrial fibrillation and syncope, 1 AF and SVT, 2 myocardial infarctions, 1 cardiac failure, 1 cardiac disorder, 1 gastrointestinal haemorrhage, 1 intestinal obstruction, 1 glaucoma, 1 cholestatic jaundice and, 1 abnormal liver function test (LFT) and 2 increased GGT, 1 bladder cancer and 1 lymphoma, 1 dysarthria, 3 strokes, 2 convulsions, 1 nephrotic syndrome, 1 renal failure, 1 angioedema (also taking an ACE Inhibitor), 1 suicide post rotigotine recall, 2 sleep attacks, 25 cases of hallucinations. A poster presentation indicated increased eating and nocturnal food craving in patients with RLS.

Summary of post-marketing experience

Post marketing safety data to date are similar to clinical trial data and the Risk Management Plan (see *Section V*) acknowledges the need to further detail risks associated with treatment of RLS with rotigotine, especially possible augmentation and rebound.

Clinical Summary and Conclusions

The two Phase III clinical trials, with 941 subjects with moderate to severe RLS treated for 6 months, provide adequate evidence of clinical efficacy, at doses of 1 mg, 2 mg and 3 mg/24 hours. The results are clinically relevant, despite a noticeable placebo response, and are supported by secondary outcome measures and the other clinical trials. The treatment efficacy is maintained over a duration of up to 3 years without a corresponding need to increase dose.

Despite improvement in RLS symptoms, there was a significant risk of treatment discontinuation (over 30% of subjects) and discontinuation due to adverse events occurred in 17% of subjects during 1 year open label treatment and 26% in 3 years open label treatment. There were no additional safety concerns over what is known from the Parkinson's disease population, with most adverse events being related to the transdermal patch or class effects of dopamine agonists. It is noted that the dose in RLS is lower than in Parkinson's disease (a maximum of 3 mg/24 h compared to 8 mg/24 h).

Risk benefit analysis

RLS is a frequently occurring neurological condition which, whilst not life-threatening, can have profound effects on a patient's sleep and daily life. Rotigotine results in good symptom reduction, increasing with increasing dose, in those with moderate to severe disease and does not appear to carry the risk of symptom augmentation. There is a significant risk of adverse effects, which also increases with increasing dose and frequently leads to treatment cessation. These risks have been adequately outlined in the proposed Product Information. It is recommended that regular assessments of efficacy, possible augmentation and adverse effects be carried out to ensure treatment benefit continues to outweigh adverse effect risks.

Submitted data limitations

The evaluator commented that:

- The data cut off of 31 January 2007 is over 2 years prior to the submission receipt at TGA (13 July 2009) and results in a lack of data beyond 3 years of open label treatment and incompleteness in the pooled safety data from open label studies. These pooled long term data should be provided.
- The risk of rebound symptoms on treatment cessation have not been assessed adequately.
- The product information should include more details on clinical trial results and information on post-marketing adverse reaction experience.

Recommendations

Based on the data provided in this submission, the evaluator recommended that rotigotine (patch strengths of 1 mg/24 h, 2 mg/24 h and 3 mg/24 h) be approved for the "symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults". However, the approval should be subject to incorporation of suggested changes to the proposed Product Information (PI).

In their responses to the clinical evaluation and Delegate's overview the sponsor referenced recent PSUR data confirming the safety profile provided in the proposed PI and argued that recent data from open label extension study SP710 had adequately investigated the risk of rebound symptoms. The revised PI included with the response included a more detailed description on clinical trials and post-marketing adverse reaction experience.

V. Pharmacovigilance Findings

Risk Management Plan

A Risk Management Plan dated 18 April 2008 was reviewed by the clinical evaluators. This has been submitted to the EU Health Authorities. A summary of the major risks with rotigotine that have been included in the proposed Australian Product Information are included in Table 18. All main identified and potential risks have been covered in the product information.

Apart from ongoing routine pharmacovigilance, the sponsor is conducting a post authorisation surveillance study (SP854) in Parkinson's disease patients and as of 3 March 2009, 550 (of a planned 2000) patients were enrolled (343 on rotigotine).[8] There is also an independent study currently being conducted in Germany examining cardiac fibrosis in Parkinson's disease patients on dopamine agonists (including rotigotine).

The plan acknowledges that an ongoing assessment of rebound and augmentation in RLS needs to be made from routine pharmacovigilance data and from data arising from the ongoing open label trial SP710. An amended SP710 protocol will assess rebound with results expected in Q1 2010.

[8] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 18: Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Application site reactions	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry). • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Specific recommendations about how to reduce and manage application site reactions are provided.) • Dosage and Administration section of the PI provides important information • Listed under Adverse Effects
Sleep attacks/sudden onset of sleep	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry). Particular attention will be paid to sleep attacks (defined as events of special interest per protocol). • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Sleep attacks have been associated with Neupro; prescribers should continually reassess; dose reduction or termination may be considered.) • Warning in Precautions section of the PI. (Patients informed not to drive or engage in other activities which may place them at risk.) • Listed under Adverse Effects
Postural/orthostatic hypotension	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry) • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Dopamine agonists are associated with postural/orthostatic hypotension; recommended to monitor blood pressure.) • Listed under Adverse Effects
Impulse control and compulsive disorder	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry) • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Pathologic gambling, increased libido and hypersexuality reported with dopamine agonists and Neupro.) • Listed under Adverse Effects
Important potential risks		
Cardiovalvular Fibrosis	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry). Particular attention will be paid to	• Warning in Precautions section of the PI. (Fibrotic complications associated with ergot-derived dopaminergic agents; whether associated with non-ergot derived

Table 18 (cont.)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	cardiac valve fibrosis-related signs and symptoms (defined as events of special interest per protocol) • Additional information from ongoing clinical trials • Independent, prospective, multicenter trial on cardiac fibrosis in Parkinson's disease patients on dopamine agonists	dopamine agonists is unknown.)
Effect on retina	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry) • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Regular ophthalmologic monitoring is recommended.)
Neuroleptic malignant syndrome after abrupt withdrawal	• Routine pharmacovigilance • Postapproval safety study under conditions of routine clinical practice (long-term patient registry) • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Although not reported with Neupro, neuroleptic malignant syndrome has been reported with abrupt withdrawal of dopaminergic therapy; recommend to taper treatment.)
Augmentation in RLS	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Warning in Precautions section of the PI. (Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts.)
Rebound in RLS	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Warning in Dosage and Administration section of the PI. (Neupro should be discontinued gradually. Following this procedure, rebound was not observed.)
Important missing information		
Patients with severe hepatic impairment	• Routine pharmacovigilance	• Warning in Precautions section of the PI. (Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment).

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections in respect of chemistry, manufacturing and controls to registration of the additional strengths of Neupro transdermal patches.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetics

Summarising the pharmacokinetic findings, the evaluator stated that:

No new absorption, distribution, metabolism and elimination (ADME) data for the rotigotine transdermal patches was provided in this submission as it was expected to be similar to that observed in the transdermal patches approved for treatment of PD.

The pharmacokinetics of a single rotigotine transdermal patch 6.75 mg/15 cm^2 were bioequivalent with the combined application of 1 x 2.25 mg/5 cm^2 plus 1 x 4.5 mg/10 cm^2 rotigotine patches.

After marketing authorisation, a new polymorphic form of the drug substance rotigotine was identified. The new polymorphic form (Form 2) differed in some of the physicochemical properties from those of the original polymorphic form (Form 1). The $AUC_{(0\text{-}tz)}$ and C_{max} of rotigotine Form 2 and Form 1 were bioequivalent for 10cm^2 patches containing 4.5 mg of each Form.

Oestradiol, LH, and FSH serum concentrations were sufficiently suppressed by a hormonal contraceptive at all time points measured, regardless of whether subjects were treated with 6.75 mg rotigotine or placebo patch. In addition rotigotine had little effect on levonorgestrel PKs, whereas the geometric means of $AUC_{(0\text{-}24),ss}$ and $C_{max,ss}$ of ethinyloestradiol were slightly higher following rotigotine treatment than placebo.

Co-administration of omeprazole, a selective inhibitor of CYP2C19, had little effect on the PKs of unconjugated and total rotigotine or its N-desalkyl metabolites.

The final population PK model for rotigotine in subjects with idiopathic RLS receiving different transdermal doses of rotigotine was a 1-compartment model with inter-individual variability described on the PK parameters CL/f and V/f with weight as a scaling factor. Age and gender were not significant covariates, nor was the site of application. However, for the application sites of abdomen, thigh, hip and flank only a small number of valid records existed ($n<28$ for each site) and the effects of these application sites on rotigotine pharmacokinetics could not be interpreted reliably.

$AUC_{(0\text{-}24),ss}$ and $C_{max,ss}$ increased dose proportionally for both unconjugated and total rotigotine

No correlation between the plasma concentrations of unconjugated rotigotine and time-matched changes from Baseline in QTcI or QTcIf were identified.

Efficacy

The evaluator identified two pivotal Phase III efficacy studies: **SP790 and SP792**.

Study SP790 - A multicentre, randomised, double-blind, placebo controlled, 4-arm parallel-group trial to investigate the efficacy and safety of 3 different transdermal doses of rotigotine in subjects with idiopathic RLS. Subjects' inclusion into the trial required the diagnosis of idiopathic restless legs syndrome based on the IRLSSG 4 essential criteria. In addition, subjects needed to have RLS of moderate or severe intensity (score of≥15) as based on the IRLS and be moderately ill as based on the CGI Item 1 (score≥4 points).

The primary efficacy outcome was assessed by the absolute change from baseline at the end of the 6 months maintenance period in the IRLS sum score and the CGI-Item 1 Severity of Illness score. Both variables were included together as primary criteria following feedback from the US FDA.

The main secondary efficacy variables were: IRLS Responder (defined as a subject with a decrease of ≥50% in IRLS sum score from baseline at the end of the maintenance period); CGI-Item 1 Responder (defined as a subject with a decrease of ≥50% in CGI-Item 1 at the end of the maintenance period); changes in CGI Items 2 and 3 during the Maintenance Period; change from baseline in individual items on the RLS-6 Rating Scales (a rating of RLS severity using 6 subscales) at the end of the maintenance period; and the Global Subject Rating of Efficacy.

Clinically significant results were predefined as a reduction of 5 points or more (indicating improvement) in the IRLS sum score and 0.75 points in the CGI Item 1. Statistical analysis included an analysis of covariance (ANCOVA) for the changes from baseline to end of the maintenance period with rotigotine dose level or placebo as the main factor, Baseline as a covariate, and centre /region/country (if applicable) as a factor. From this ANCOVA, treatment least squares (LS) means (with 95% confidence intervals [CI]) were calculated and 1-sided 2-sample t-tests were performed (significance level 0.025) to demonstrate superiority of the rotigotine dose level versus placebo, starting with 6.75 mg/day.

The Full Analysis Set (FAS) with last observation carried forward (LOCF) was considered the primary analysis set for the outcome of the trial. It included all randomized subjects with baseline values and at least 1 valid post-baseline value under treatment for the primary variables (IRLS sum score and CGI-Item 1). Significant results for both co-primary endpoints were required to demonstrate superiority of the rotigotine dose level over placebo.

Study SP792 –A multi-centre, randomised, double-blind, placebo-controlled, 5-arm parallel-group trial to investigate the efficacy and safety of 4 different transdermal doses of rotigotine in subjects with idiopathic RLS. Subjects' inclusion in the trial were as per SP790 and so was the design with a 4 week titration period (one week longer than in SP790 to allow for the additional lower dose), as 505 eligible subjects (mean age 52.3 years) were randomised into 1 of 5 groups (rather than 4). The additional lower dose of 1.125 mg/day was included to establish a minimum effective dose as per feedback from the US FDA.

Primary and secondary efficacy outcome variables were the same as in SP790. The sample size, power calculation and statistical analysis were the same as SP790.

The evaluator identified three supporting short term studies **SP666, SP709 and SP794**.

Study SP666- A multi-centre, randomised, double-blind, placebo-controlled, four-arm parallel-group trial of rotigotine in patients with idiopathic RLS (Phase IIa). Subjects' inclusion into the trial required the diagnosis of RLS as per the IRLSSG four essential features and a minimum score of ≥ 5 on the IRLS Sum score if on L -dopa, or ≥ 10 if untreated, and a score of ≥ 3 for severity of RLS during the day. Subjects also needed to show response to treatment with dopaminergic medication if they had previously received this treatment.

The primary endpoint was the absolute change from baseline to end of treatment in the IRLS sum score, comparing three doses of rotigotine with placebo. As this was a pilot study, no sample size or power calculations were carried out. Descriptive analyses were carried out with the FAS, giving summary statistics, 95% confidence intervals and p-values, in conjunction with an analysis of covariance model (ANCOVA) where treatment groups were included as the main factor and baseline IRLS score as a covariate.

Study SP709 - A phase IIb multi-centre, double-blind, randomized, placebo-controlled, six-arm, parallel-group, dose-finding trial to determine efficacy, safety and tolerability of five different transdermal doses of rotigotine (1.125 mg, 2.25 mg, 4.5 mg, 6.75 mg, and 9.0 mg) in idiopathic RLS. Following on from positive results with 4.5 mg in the phase IIa (SP666) trial, two higher doses (6.75 mg and 9.0 mg/day) were included in this trial for further investigation.

The primary efficacy variable was absolute change in the IRLS sum score from baseline to the end of the maintenance period.

Study SP794- A multicentre, double-blind, randomized, placebo-controlled, two-arm, parallel-group, sleep laboratory trial to investigate the efficacy and safety of transdermal rotigotine in subjects with idiopathic RLS. The study included subjects with the diagnosis of idiopathic RLS who also satisfied the following criteria: (1) either had no previous treatment for RLS or have had initial response to previous dopaminergic treatment; (2) have a score of IRLS score of≥15 at baseline; (3) CGI-Item I score of ≥4 points at baseline; and (4) have a Periodic Limb Movement Index (PLMI; periodic limb movements [PLMs]/total time in bed [TIB]) of ≥15 based on polysomnography (PSG) as assessed by the investigator.

The primary efficacy outcome was assessed by the reduction of the PLMI at the end of the maintenance period compared to baseline. PLMI (PLMs /TIB) data was obtained from PSGs which were evaluated at a central reading laboratory.

The following secondary variables were measured as change from baseline at the end of the maintenance period: PLMSAI (Periodic Limb Movements during Sleep Arousal Index = PLMs during sleep with arousals/total sleep time); Sleep efficiency (%; sleep time/TIB); IRLS sum score, CGI-Item 1 (Severity of Illness); and MOS Sleep Scale-Adequacy Subscale.

The primary analysis was an analysis of covariance (ANCOVA) of the log-transformed PLMI at the end of the maintenance period.

The evaluator identified three supporting open label long term studies: **SP710 and SP793**.

Study SP 710- An open label extension trial to determine safety and tolerability of long-term transdermal application of rotigotine in subjects with idiopathic RLS. It was an extension of the phase IIb study (SP709). As the final study report was not available, data were supplied in 3 interim reports: Year 1, Year 2 and Year 3 (patient data to February 2007). The trial commenced mid 2003 and planned to run for 5 years or until rotigotine is commercially available. Subjects who had completed study SP709 and who were compliant without any severe application site reaction were eligible.

Study SP791- A one year multi-centre, open-label extension trial to assess safety and tolerability of rotigotine in subjects with idiopathic RLS, who had successfully completed the maintenance periods and the taper periods of SP790 (6 month phase III trial) or SP794 (sleep laboratory trial).

Study SP793– A one year multi-centre, open-label extension trial in subjects who had completed the maintenance and taper period of SP792 (6 month phase III double blind trial).

Regarding efficacy, the evaluator summarised that:

In the two pivotal Phase III trials (SP790 and SP792), two co-primary efficacy endpoints were evaluated: the sum score of the patient-rated Restless Legs Syndrome Rating Scale (IRLS) and physician-rated Clinical Global Impression (CGI) Item 1 Severity of Illness score. Both scales are internationally recognised for assessing efficacy of RLS treatments. Doses of 2.25 mg/day, 4.5 mg/day and 6.75 mg/day all showed statistically significant efficacy over placebo in reductions of these two scores after approximately 7 months of treatment. Trends suggesting dose-dependent response was also evident with greater reductions in symptoms and illness severity with higher doses. The dose of 1.125 mg/day did not demonstrate significant change compared to placebo.

Treatment response was greater in the European trial SP790 (net treatment effect of rotigotine over placebo was -5.1 to -8.2 for IRLS sum score, and -0.8 to -1.2 for CGI-Item 1) compared to the US trial SP9792 (-2.2 to -5.2 for IRLS sum score and -0.35 to -0.9 for CGI-Item 1). This may be explained by more severe disease in the SP790 subjects with baseline IRLS scores of 28 to 28.2 compared to baseline IRLS scores of 23.1 to 23.6 in study SP792.

Supportive evidence of efficacy was also provided by the 2 Phase II studies which used the IRLS sum score as the primary efficacy endpoint. In the Phase IIa trial SP666, the dose of 4.5 mg/day showed a statistically significant treatment difference to placebo. In the Phase IIb study (SP709), a dose response was evident and treatment difference between rotigotine and placebo was significant for doses of 2.25 mg, 4.5 mg, 6.75 mg and 9 mg/day, although the highest dose (9 mg/day) showed no additional benefit over the preceding dose of 6.75 mg.

A sleep laboratory study which measured period limb movements as the primary endpoint demonstrated that rotigotine was significantly more effective than placebo in the reduction of the PLMI at the end of a 7 week treatment period.

Long term efficacy data, whilst not the primary outcome, were examined from 3 open label long term safety studies involving 955 patients. Symptom reduction was maintained after an additional 1 year (SP791 and SP793) and 3 years (SP710) of treatment. Increases in rotigotine dose during 3 years of open label treatment were modest.

A greater treatment effect was seen in females, in those with more severe disease at study onset, and in those who had been previously treated with other RLS therapies. Age, tobacco use and alcohol use did not alter treatment effect.

Safety

The evaluator summarised that:

As similar safety results were seen on the two Phase III randomised controlled trials (SP790 and SP792) safety was assessed from the primary safety database of pooled data. This contained data from 748 subjects treated with rotigotine for a mean duration of about 6 months (167 days). This was supplemented by data from 3 open label extension studies with 914 subjects treated for about 1 year (mean 418 days). The database cut-off was 31 January 2007. These databases were sufficient in terms of patient numbers and treatment duration to undertake a primary safety assessment.

Compared to placebo, the incidence of AEs (rotigotine vs placebo: 83% vs 68%), SAEs (6% vs 4%) and discontinuations due to AEs (18% vs 6%) were more frequent in rotigotine-treated subjects. The transdermal patch delivery system was the most frequent cause of AEs (34% of rotigotine-treated subjects vs 4% in placebo). In addition, 1% of all rotigotine-treated subjects had a reaction severe enough to be classed as an SAE (the most frequent cause of an SAE). As with other dopamine agonists, frequent AEs were nausea (19%), headache (17%),

fatigue (11%), somnolence (8%), dizziness (7%), and sleep disorders (5%). Such AEs also showed dose-related trends. Medication intolerance, particularly with increasing dose, was moderate. Eighteen per cent of all rotigotine subjects had an adverse event leading to ceasing the medication (compared to 6% of placebo subjects). Again the main reasons for stopping medication were patch site reactions, nausea, dizziness and fatigue.

Specific adverse events that occurred more frequently in those taking rotigotine were compulsive behaviour (3% vs <1%), sleep attacks (2% vs <1%), syncope (1% vs <1%) and valvulopathy (<1% vs 0%). There was no greater incidence of orthostatic hypotension, falls, arrhythmias or fibrosis. There were two cases of valvulopathy (aortic stenosis and incompetence). The subject with aortic stenosis was diagnosed after 57 days of rotigotine exposure and died post surgery.

Haematology, clinical chemistry and urinalysis investigations were not remarkable. As is seen with dopamine agonists, prolactin levels were seen to decrease. Whilst there was no greater incidence of severe orthostatic hypotension, 1% of rotigotine subjects had an AE of syncope compared to <1% of placebo subjects. ECG findings were unremarkable and a Thorough QT/QTc study" in Parkinson's disease patients did not show any evidence of QTc prolongation at doses up to 24 mg/24 hours.[9]

Conclusions regarding treatment in a non-Caucasian population cannot be made due to lack of such subjects in the database. Whilst there were 3 pregnancies reported no conclusions can be drawn on the effect of treatment in pregnant women. There were no specific safety issues in subgroup analysis by age, gender, or concomitant disease.

Augmentation (worsening of symptoms during treatment) was assessed at early withdrawal and after 6 months of treatment and was not more evident compared to placebo. Rebound was only assessed in a limited population (33 rotigotine subjects) and whilst it did not suggest symptom increase on treatment cessation, this population is too small to make a meaningful conclusion.

The longer term safety analysis (data for an additional 1 year of treatment) showed safety results similar to those observed following short term treatment with rotigotine.

The evaluator reviewed the submitted post marketing data and summarised that the post marketing safety data to date are similar to clinical trial.

Risk Management Plan

The clinical evaluator reviewed the Risk Management Plan (RMP) submitted by the sponsor and summarised that the RMP acknowledges the need to further detail the risks associated with treatment of RLS with rotigotine, especially possible augmentation and rebound effects.

Risk-Benefit Analysis

The Delegate found no issues or concerns identified with the newly sought strengths of rotigotine (Neupro) transdermal patches and proposed to recommend for approval:

- The extension of indications sought, that is:

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults, and

[9] EMEA. ICH E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, 25 May 2005. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04).

- The new strengths sought, that is: Rotigotine (Neupro) transdermal 1 mg/ 24h and 3 mg/ 24h patches.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following indication:

The symptomatic treatment of moderate to severe idiopathic Restless Leg Syndrome in adults.

In making this recommendation the ACPM agreed with the Delegate that evidence of the safety and efficacy of the formulation and the dosage regimen was sufficient to support the extension of the indication and register the new strengths for rotigotine. The ACPM noted that the efficacy data demonstrated a significant placebo effect and that the PI and CMI should be strengthened to ensure the appropriate inclusion of the risk of sudden somnolence, particularly in view of the anticipated younger population group for this indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Neupro rotigotine 1 mg/24 h transdermal patches sachet and Neupro rotigotine 3 mg/ 24h transdermal patches sachet.

TGA also approved the extension of indications for Neupro (rotigotine) transdermal patches 2 mg/24 h, 4 mg/24 h, 6 mg/24 h, 8 mg/24 h and the two new strengths (1 mg/24 h and 3 mg/24 h) indicated for:

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.

For the current Product Information please refer to the TGA website at www.tga.gov.au.

Neupro® (rotigotine) transdermal patches

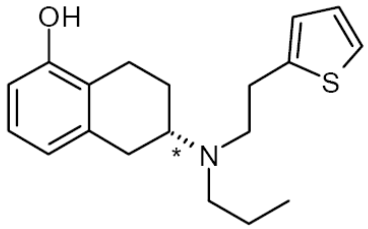
NAME OF THE MEDICINE

NEUPRO® rotigotine transdermal patch

Neupro 1 mg/24h
Neupro 2 mg/24 h
Neupro 3mg/24h
Neupro 4 mg/24 h
Neupro 6 mg/24 h
Neupro 8 mg/24 h

Chemical name: (6S)-6-{propyl-[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol

Chemical structure:



Molecular formula: $C_{19}H_{25}NOS$

MW: 315.48

CAS number: [99755-59-6]

DESCRIPTION

The active ingredient rotigotine is a white to light brownish powder. It is very slightly soluble to freely soluble in organic solvents, sparingly soluble in acidic aqueous solutions and practically insoluble in alkaline aqueous solutions.

Neupro is a thin, matrix-type transdermal patch composed of 3 layers:

1. A flexible, tan-colored backfilm that provides structural support and protection of the drug-loaded adhesive layer

2. A self-adhesive drug matrix layer. The excipients contained in the self adhesive matrix are povidone, ascorbyl palmitate, dl-alpha tocopherol and sodium metabisulfite. The adhesive matrix consists of a mixture of two proprietary silicone adhesives (BIO-PSA Q7-4301 and BIO-PSA Q7-4201).

3. A clear protective liner which is removed prior to use.

PHARMACOLOGY

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopamine receptor agonist for the treatment of Parkinson's disease. It is believed to elicit its beneficial effect by activation of the D_3, D_2 and D_1 receptors in the brain. Several rotigotine metabolites share its pharmacological activity at dopamine receptors. Rotigotine also has agonist activity at α_{1A} adrenoceptors and 5-HT_{1D} receptors. Rotigotine improved motor deficits in animal models of Parkinson's disease.

Pharmacokinetics

Absorption
Following application, rotigotine is continuously released from the transdermal patch and absorbed through the skin. Steady-state concentrations are reached after one to two days of patch application and are maintained at a stable level by once daily application in which the patch is worn for 24 hours. Rotigotine plasma concentration increases dose-proportionally over a dose range of 1 mg/24 h to 24 mg/24 h.

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal application is approximately 37%.

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 1% (hip versus abdomen) to 46% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

Because the patch is administered transdermally, no effect of food and gastrointestinal conditions is expected.

Distribution
The *in vitro* binding of rotigotine to plasma proteins is approximately 92%. The apparent volume of distribution in humans is approximately 84 L/kg.

Metabolism
Rotigotine is extensively metabolised by N-dealkylation as well as direct and secondary conjugation. *In vitro* results indicate that different CYP isoforms are able to catalyse the N-desalkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl-metabolites.

The information on metabolites is incomplete.

Elimination
Approximately 71% of the rotigotine dose is excreted in urine and a smaller part of about 23% is excreted in faeces. The clearance of rotigotine after transdermal administration is approximately 10 L/min and its elimination half-life is 5 to 7 hours.

Special patient groups
Because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the dose based on gender, weight, race or age is not necessary.

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

CLINICAL TRIALS

Parkinson's disease

The effectiveness of Neupro in the treatment for the signs and symptoms of idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of four pivotal, Phase III, parallel, randomized, double-blind placebo controlled studies.

Two trials investigating the effectiveness of Neupro for the treatment of idiopathic Parkinson's disease were conducted in patients with early stage Parkinson's disease who were not receiving concomitant dopamine agonist therapy and were either levodopa naïve or previous levodopa treatment was ≤ 6 months.

The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Efficacy was determined by the subject's response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III).

Two additional trials were conducted in patients with advanced idiopathic Parkinson's disease who were receiving concomitant levodopa therapy.

The primary outcome assessment was the reduction in "off" time (hours). Efficacy was determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

Clinical Trials of Neupro in Early Stage Disease

In a double blind study, 177 patients received Neupro and 96 patients received placebo. The patients were titrated to their optimal dose of Neupro or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Onset of treatment benefits began as early as the second week of treatment. Patients were maintained at their optimal dose for 6 months.

For 91% of the subjects in the Neupro arm , the optimal dose was the maximal dose allowed i.e. 6 mg/24 h at the end of the maintenance treatment. An improvement of 20% was seen in 48% of the subjects receiving Neupro and in 19% of the subjects receiving placebo (difference 29% $CI_{95\%}$ 18%; 39%, $p<0.0001$). With Neupro, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points) The difference from placebo was 5.28 points and statistically significant ($p<0.0001$).

In a second double-blind study, 213 patients received Neupro, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of Neupro in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4

weeks. In the ropinirole group, patients were titrated to their optimal dose up to a maximum of 24 mg/day over 13 weeks. Patients in each treatment group were maintained for 6 months.

At the end of the maintenance treatment in 92% of the subjects in the Neupro arm the optimal dose was the maximal dose allowed i.e. 8 mg/24 h at the end of the maintenance treatment. An improvement over baseline of 20% was seen in 52% of the subjects receiving Neupro, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (difference Neupro versus placebo 21.7%; $CI_{95\%}$ 11.1% ; 32.4%, difference ropinirole versus placebo 38.4% $CI_{95\%}$ 28.1% ; 48.6% , difference ropinirole versus rotigotine 16.6%; $CI_{95\%}$ 7.6% ; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was -6.83 points (baseline 33.2 points) in the Neupro arm, -10.78 points in the ropinirole arm (baseline 32.2 points) and -2.33 points in the placebo arm (baseline 31.3 points). All differences between the active treatments and placebo were statistically significant.

Clinical Trials of Neupro in Advanced Disease

In a double blind study, 113 patients received Neupro in conjunction with levodopa up to a maximum dose of 8 mg/24 h, 109 patients received Neupro up to a maximum dose of 12 mg/24 h and 119 patients received placebo. The patients were titrated to their optimal doses of Neupro or placebo in weekly increments of 2 mg/24 h starting at 4 mg/24h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance period an improvement of at least 30% was seen in 57% and 55% of the subjects receiving Neupro 8 mg/24 h and 12 mg/24 h, respectively and in 34% of the subjects receiving placebo (Differences 22% and 21%, respectively $CI_{95\%}$ 10%; 35% and 8%; 33%, respectively, $p<0.001$ for both Neupro groups). With Neupro, the mean reductions in "off" time were 2.7 and 2.1 hours, respectively whereas in the placebo-treated arm a reduction of 0.9 hours was observed. The differences were statistically significant ($p<0.001$ and $p=0.003$, respectively).

In a second double-blind study, 201 patients received Neupro, 200 received pramipexole, and 100 patients received placebo. All patients were also receiving levodopa. The patients were titrated to their optimal dose of Neupro in weekly increments of 2 mg/24 h starting at 4 mg/24 h to a maximum dose of 16 mg/24 h. In the pramipexole group, patients received 0.375 mg in the first week, 0.75 mg in the second week and were titrated further in weekly increments of 0.75 mg to their optimal dose up to a maximum of 4.5 mg/day. Patients in each treatment group were maintained for 4 months.

At the end of the maintenance treatment an improvement of at least 30% was seen in 60% of the subjects receiving Neupro, 67% of the subjects receiving pramipexole and 35% of the subjects receiving placebo (Difference Neupro versus placebo 25%; $CI_{95\%}$ 13%; 36%, difference pramipexole versus placebo 32% $CI_{95\%}$ 21% ; 43% , difference pramipexole versus rotigotine 7%; $CI_{95\%}$ -2% ; 17%).The mean reduction in the "off" time was 2.5 hours in the Neupro arm, 2.8 hours in the pramipexole arm, and 0.9 hours in the placebo arm. All differences between the active treatments and placebo were statistically significant.

Restless Legs Syndrome

The effectiveness of Neupro in the treatment of moderate to severe idiopathic RLS was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double-blind, placebo-controlled studies and a placebo-controlled, optimal dose sleep lab trial.

The primary outcome assessment in the two pivotal trials was the absolute change from baseline at the end of the maintenance period in the International RLS Study Group Rating Scale (IRLS) sum score and the Clinical Global Impression (CGI) Item 1 score (Severity of Illness).

The primary objective of the first double-blind trial (SP790) was to demonstrate efficacy of 3 different transdermal doses of Neupro (1, 2 and 3 mg/24 h) versus placebo in subjects with moderate to severe idiopathic RLS over a 6-month maintenance period. A total of 333 patients received rotigotine in the three active treatment arms and 114 patients received placebo. At the end of maintenance both efficacy variables showed clinically relevant efficacy for all 3 rotigotine doses tested. (See Table 1.)

The primary objective of the second double-blind trial (SP792) was to demonstrate efficacy of 4 different transdermal doses of Neupro (0.5, 1, 2 and 3 mg/24 h) versus placebo in subjects with moderate to severe idiopathic RLS over a 6-month maintenance period. A total of 395 patients received rotigotine in the 4 active treatment arms and 99 patients received placebo. At the end of maintenance both efficacy variables showed clinically relevant efficacy of rotigotine 2 mg/24 h and 3 mg/24 h. (See Table 1.)

Table 1 Neupro - Change from Baseline to End of Maintenance Period

	Study SP790			
	Neupro 1 mg/24 h	**Neupro 2 mg/24 h**	**Neupro 3 mg/24 h**	**Placebo**
IRLS Sum Score				
Number of patients	112	109	112	114
LS Mean	-13.7	-16.2	-16.8	-8.6
Difference to placebo	-5.1	-7.5	-8.2	
(95% CI)	(-7.6, -2.7)	(-10.0, -5.1)	(-10.6, -5.7)	
p-value	<0.0001	<0.0001	<0.0001	
CGI Item 1				
Number of patients	112	109	112	114
LS Mean	-2.09	-2.41	-2.55	-1.34
Difference to placebo	-0.76	-1.07	-1.21	
(95% CI)	(-1.13, -0.38)	(-1.44, -0.69)	(-1.58, -0.83)	
p-value	<0.0001	<0.0001	<0.0001	

	Study SP792				
	Neupro 0.5 mg/24 h	**Neupro 1 mg/24 h**	**Neupro 2 mg/24 h**	**Neupro 3 mg/24 h**	**Placebo**
IRLS Sum Score					
Number of patients	98	99	95	103	99
LS Mean	-11.1	-11.2	-13.5	-14.2	-9.0
Difference to placebo	-2.2	-2.3	-4.5	-5.2	
(95% CI)	(-4.5, 0.2)	(-4.6, 0.0)	(-6.9, -2.2)	(-7.5, -2.9)	
p-value	0.0682	0.0535	0.0002	<0.0001	
CGI Item 1					
Number of patients	98	99	95	103	99
LS Mean	-1.75	-1.72,	-2.05	-2.31	-1.40
Difference to placebo	-0.35	-0.32	-0.65	-0.90	
(95% CI)	(-0.72, 0.02)	(-0.69, 0.05)	(-1.02, -0.28)	(-1.27, -0.54)	
p-value	0.0603	0.0857	0.0007	<0.0001	

LS Mean = least squares mean

In a third study (SP794) patients were investigated in a sleep lab setting. The objective of the double-blind phase 3 sleep lab trial was to demonstrate that rotigotine is effective in subjects with moderate to severe idiopathic RLS based on the Periodic Limb Movement Index (PLMI; PLMs/total time in bed) as measured by polysomnography (PSG). The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 1 mg/24 h starting at 1 mg/24 h to a maximum dose of 3 mg/24 h. Patients were maintained at their optimal dose for 4 weeks. Efficacy was assessed by the PLMI at the end of the maintenance period compared to baseline. A total of 46 patients received rotigotine treatment and 20 patients received placebo. The efficacy of Neupro over placebo was demonstrated for the primary efficacy variable. The PLMI decreased from 50.9 at baseline to 7.7 with rotigotine treatment and from 37.4 to 32.7 with placebo ($p<0.001$). Rotigotine was 4.25 times more effective than placebo in the reduction of the PLMI at the end of the maintenance period.

INDICATIONS

Parkinson's disease
Neupro is indicated as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease.

Restless Legs Syndrome
Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

CONTRAINDICATIONS

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

Magnetic resonance imaging or cardioversion (see PRECAUTIONS).

PRECAUTIONS

The backing layer of Neupro contains aluminium. To avoid skin burns, Neupro should be removed if the patient has to undergo magnetic resonance imaging (MRI) or cardioversion.

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, however the incidence was similar to that in placebo-treated patients.

Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.

It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

As with other dopamine agonists, Neupro was associated with the development of peripheral edema in some patients with Parkinson's disease.

Somnolence and Sudden Onset of Sleep: Patients treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some perceived no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment.

Somnolence is a common occurrence in patients receiving Neupro. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with Neupro. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with Neupro.

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops meaningful daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued (see DOSAGE AND ADMINISTRATION for guidance on discontinuing Neupro).If a decision is made to continue Neupro, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Because of possible additive effects, patients should be advised to exercise caution when taking sedating medicinal products or other CNS (central nervous system) depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with Neupro (see "Interaction with other medicines").

Placebo-controlled trials have shown a higher incidence of visual disturbance and eye conditions (see ADVERSE EFFECTS) in the rotigotine groups in comparison with controls. Similar events have been observed in open-label trials. It is important to carry out ophthalmologic monitoring at regular intervals for early detection of visual abnormalities.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see DOSAGE AND ADMINISTRATION).

Hallucinations have been reported and patients should be informed that hallucinations can occur.

Neuroleptics given as antiemetic should not be given to patients taking dopamine agonists (see PRECAUTIONS – Interactions with other medicines).

Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts.

External heat (excessive sunlight, heating pads and other sources of heat such as sauna, hot bath) should not be applied to the area of the patch.

Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted.

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Rotigotine transdermal patch contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see PHARMACOLOGY – Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Fibrotic complications: Neupro is a non-ergot derived dopaminergic agent.

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, non-ergot derived dopamine agonists can cause them is unknown.

Cardiac valve abnormalities have been observed in open-label trials of rotigotine, however in placebo-controlled clinical trials, the incidence of these adverse events was similar between treatment groups. Regular cardiac review as part of physical examination should be performed. Echo-cardiograph monitoring may be advisable in accordance with clinical judgement. (see ADVERSE EFFECTS)

Special precaution for disposal: After use the patch still contains active substance. After removal, the used patch should be folded in half, adhesive side inwards so that the matrix layer is not exposed, placed in the original sachet and then discarded out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

Effects on fertility

Subcutaneous administration of rotigotine to male rats prior to and through mating did not affect fertility, although epididymal sperm motility was reduced at a plasma rotigotine concentration 11-fold the clinical plasma C_{max} at the maximal recommended dose; the no-effect dose was 4-fold the clinical C_{max}. In female mice and rats, rotigotine disrupted implantation and prevented pregnancy, probably due to hypoprolactinaemia. These effects are considered not clinically relevant because, in humans, chorionic gonadotropin rather than prolactin is essential for implantation.

Use in Pregnancy

Category: B3

There are no adequate data on the use of Neupro in pregnant women. Subcutaneous administration of rotigotine to mice, rats and rabbits during the period of organogenisis did not produce teratogenicity. Maternotoxic doses were associated with embryofetal toxicity. Administration to rats from early gestation to weaning was associated with effects in offspring (impaired auditory startle reflex during lactation, delays in some developmental indices). The potential risk for humans is unknown. Rotigotine should not be used during pregnancy.

Use in lactation

Because rotigotine decreases prolactin secretion in humans, inhibition of lactation is expected. Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. Subcutaneous administration to rats from early gestation to weaning was associated with adverse effects in offspring (see **Use in Pregnancy**). In the absence of human data, breast-feeding should be discontinued.

Paediatric use

Neupro is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Use in the elderly

No dosage adjustment is necessary in the elderly because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect (see PHARMACOLOGY – Pharmacokinetics)

Carcinogenicity

Two-year subcutaneous carcinogenicity studies with rotigotine were conducted in mice and rats, achieving respective systemic exposures (plasma AUC) up to 5- and 2-fold the clinical plasma AUC at the maximal recommended dose. There was no evidence of carcinogenicity in mice. Rats developed Leydig cell adenomas and uterine tumours (adenocarcinomas, squamous cell carcinomas), but the findings are of questionable significance because the endocrine mechanisms are not considered relevant to humans.

Ocular Toxicity

After a single dose of rotigotine, binding to melanin-containing tissues (eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period. Retinal degeneration was observed by transmission microscopy following subcutaneous administration of rotigotine to albino rats for 3 months. The effects were more pronounced in females. Additional studies to further evaluate the specific pathology have not been performed. Retinal degeneration was not observed during the routine histopathological evaluation of the eyes in any of the toxicology studies in any species used. The relevance of these findings to humans is not known.

Genotoxicity

There was no evidence of genotoxicity in assays for bacterial gene mutation and unscheduled DNA synthesis in rat hepatocytes. A positive result was obtained in the *in vitro* mouse lymphoma assay, but there was no evidence of clastogenicity in the *in vivo* mouse micronucleus assay.

Interactions with other medicines

Because rotigotine is a dopamine agonist, it is assumed that dopamine antagonists, such as neuroleptics (e.g. phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Neupro, and co-administration should be avoided. Because of possible additive effects, caution should be advised when patients are taking sedating medicinal products or other CNS (central nervous system) depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with Neupro.

Co-administration of enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/Hypericum perforatum) has not been investigated.

Co-administration of levodopa and carbidopa with rotigotine had no effect on the pharmacokinetics of rotigotine, and rotigotine had no effect on the pharmacokinetics of levodopa and carbidopa.

Neupro may potentiate the dopaminergic adverse reaction of levodopa and may cause and/or exacerbate pre-existing dyskinesia, as described with other dopamine agonists.

The incidence of some dopaminergic adverse effects, such as hallucinations, dyskinesia, and peripheral oedema generally is higher when given in combination with levodopa.

Rotigotine is primarily metabolized by, and also inhibits to a degree, CYP2C19. Co-administration of rotigotine and drugs that are metabolised by CYP2C19 may lead to an increase systemic exposure to these drugs. This has not been fully characterised, however some *in vitro* and *in vivo* studies suggest that the inhibition of CYP2C19 may only be clinically relevant at supra-therapeutic doses. 50% inhibition was observed in one *in vitro* study at concentrations 80-fold higher than maximum plasma concentrations observed for the dose of 16 mg/24 h. Possible interaction should be borne in mind when co-administering other drugs metabolized by CYP2C19.

Co-administration of domperidone with rotigotine had no effect on the pharmacokinetics of rotigotine.

Co-administration of omeprazole (inhibitor of CYP2C19), in doses of 40 mg/day, had no effect on the pharmacokinetics and metabolism of rotigotine in healthy volunteers.

Co-administration of rotigotine (3 mg/24h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel).

Interactions with other forms of hormonal contraception have not been investigated.

Effect on laboratory tests

As seen in other dopamine agonists, clinical trials revealed a decrease of prolactin plasma concentrations after exposure to rotigotine.

Effects on ability to drive and use machines

Neupro may have a major influence on the ability to drive and use machines (see ADVERSE EFFECTS).

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. Patients being treated with Neupro and presenting with somnolence and/or sudden sleep episodes must be informed not to drive or engage in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see PRECAUTIONS).

ADVERSE EFFECTS

Parkinson's disease

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1083 Neupro- and 508 placebo-treated patients, 73.0% of the patients on Neupro and 56.3% of patients on placebo reported at least one adverse reaction.

At the beginning of therapy dopaminergic adverse reactions such as nausea and vomiting may occur. These are usually mild or moderate in intensity and transient even if treatment is continued.

Adverse drug reactions (ADRs) reported in more than 10% of patients treated with Neupro transdermal patch are nausea, dizziness, somnolence and application site reactions.

In trials where the application sites were rotated as reflected in the instructions provided in the Consumer Medicine Information, 35.7% of 830 patients using the Neupro transdermal patch, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 4.3% of all subjects receiving Neupro.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table covers adverse drug reactions from all rotigotine studies in patients with Parkinson's disease.

System/organ classes (MedDRA)	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Immune system disorder			hypersensitivity	
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Perception disturbances[b] (hallucination[a], visual hallucination[a], auditory hallucination[a], illusion) confused state, abnormal dreams[a], insomnia[a]	sleep attacks[a], psychotic disorder (including paranoid psychosis), compulsive disorders (including pathologic gambling, punding), increased libido (including hypersexuality), anxiety, sleep disorder[a], nightmares, disorientation	
Nervous system disorders	somnolence[a], dizziness[a]	dyskinesia[a] headache[a] , dizziness postural, headache[a]	Syncope,vasovagal syncope, dystonia, hypersomnia, lethargia, disturbance in attention, memory impaired, paraesthesia dysgeusia, balance disorder, tremor.	Convulsion, loss of consciousness
Eye disorders			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			Atrial fibrillation, heart rate increased, palpitations	Supraventricular tachycardia
Vascular disorders		orthostatic hypotension, (see PRECAUTIONS)	Hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders			cough, hiccup[a] dyspnoea	
Gastrointestinal disorders	nausea[a],	vomiting[a], diarrhoea, constipation[a], dyspepsia[a] dry mouth[a],	abdominal pain (incl upper abdominal pain), stomach discomfort	
Hepato-biliary disorder		hepatic enzyme increased (including GGT, ALAT, ASAT)		

System/organ classes (MedDRA)	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Skin and subcutaneous tissue disorders		rash (incl. allergic; macular exanthema) (see PRECAUTIONS), erythema[a] pruritus hyperhydrosis[a],	Generalised pruritus, dermatitis contact, skin irritation,	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions[b] (including erythema[a], pruritus[a], irritation[a], burning[a], dermatitis[a], inflammation, papulae,vesicle,blister, pain, hypersensitivity) (see PRECAUTIONS)	oedema peripheral[a], asthenic conditions[b] (incl. fatigue[a], asthenia, malaise), weight decrease	Gait disturbance[a,] feeling abnormal, weight increased[a]	
Injury, poisoning and procedural complications			Fall	

[a] These adverse drug reactions have been reported in the pooled placebo-controlled trials at a frequency of 1% more than in the placebo-treated patients. See PRECAUTIONS and Effects on ability to drive and use machines
[b] High level term.

Adverse events that might be indicative of fibrosis reported in the advanced-stage PD clinical trial program are summarized below.

Rotigotine treatment-emergent adverse events related to fibrosis – Advanced-stage Parkinson's disease

MedDRA® version 8.1 High Level Term Preferred Term	Placebo-Controlled Studies		All studies (including open label studies*)
	Placebo N=219 n (%)	Rotigotine N=434 n (%)	Rotigotine N=1151 n (%)
Hydronephrosis	1 (0.5)	0	1 (<0.1)
Pleural effusion	1 (0.5)	0	1 (<0.1)
Cardiac valve disease	0	1 (0.2)	1 (<0.1)
Cardiac murmur	0	1 (0.2)	3 (0.3)
Mitral valve incompetence	0	0	5 (0.4)
Aortic valve incompetence	0	0	2 (0.2)
Aortic valve sclerosis	0	0	1 (<0.1)
Tricuspid valve incompetence	0	0	2 (0.2)

MedDRA®=Medical Dictionary for Regulatory Activities
* Patients in open label studies were on concomitant Parkinson's disease medications.

Restless Legs Syndrome

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.0% of the patients on Neupro and 32.7% of patients on placebo reported at least one adverse reaction.

At the beginning of therapy dopaminergic adverse reactions such as nausea and vomiting may occur. These are usually mild or moderate in intensity and transient even if treatment is continued.

Adverse drug reactions (ADRs) reported in more than 10% of patients treated with Neupro are nausea, application site reactions, fatigue and headache.

In trials where the application sites were rotated as reflected in the instructions provided in the SPC and package leaflet, 34.2% of 748 patients using Neupro, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

The following table covers adverse drug reactions from all studies in patients with Restless Legs Syndrome. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System/organ classes (MedDRA)	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1,000, <1/100**	**Rare ≥1/10,000, ≤1/1,000**
Gastrointestinal disorders	Nausea	Vomiting, Dyspepsia		
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, excoriation, urticaria, hypersensitivity) Fatigue	Irritability		
Immune system disorders		Hypersensitivity		
Nervous system disorders	Headache	Somnolence		
Psychiatric disorders		Sleep attacks, Sexual desire disorder[a] (incl. hypersexuality, libido increased), Insomnia, Sleep disorder, Abnormal dreams	Impulse control disorder[a] (incl. pathological gambling, punding)	Obsessive compulsive disorder

System/organ classes (MedDRA)	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, ≤1/1,000
Skin and subcutaneous tissue disorders		Pruritus		
Vascular disorders		Hypertension	Orthostatic hypotension	

a) High Level Term

Post-marketing experience: The post marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

Both Indications
Rotigotine has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases "sudden onset of sleep" occurred while driving and resulted in motor vehicle accidents.

Patients treated with dopamine agonists for treatment of Parkinson's disease, including Rotigotine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

DOSAGE AND ADMINISTRATION

Neupro is applied once a day. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application.

If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Neupro can be applied irrespective of the timing of meals.

Dosage

The dose recommendations made below are in nominal dose.

Parkinson's disease

Dosing in patients with early stage Parkinson's disease:

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

4 mg/24 h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of 6 mg/24 h or 8 mg/24 h, respectively.
The maximal dose is 8mg/24h.

Dosing in patients with advanced stage Parkinson's disease:

A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.

4 mg/24 h or 6 mg/24h may be effective doses in some patients. For most patients an effective dose is reached within 3 to7 weeks at doses of 8 up to a maximum dose of 16 mg/24 h.

For doses higher than 8 mg/24h multiple patches may be used to achieve the final dose e.g. 10 mg/24h may be reached by combination of a 6 mg/24h and a 4 mg/24h patch.

Restless Legs Syndrome

A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months for risk-benefit analysis.

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see PHARMACOLOGY – Pharmacokinetics and PRECAUTIONS). Rotigotine has not been investigated in patients with severe hepatic impairment.

Children and adolescents: Rotigotine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Treatment discontinuation

Parkinson's disease
Neupro should be discontinued gradually. The daily dose should be reduced in steps of 2 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of Neupro (see PRECAUTIONS).

Restless Legs Syndrome
Neupro should be discontinued gradually. The daily dose should be reduced in steps of 1 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of Neupro (see PRECAUTIONS). Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

Method of administration

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Neupro should not be placed on skin that is red, irritated or damaged. (see PRECAUTIONS).

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is folded back and the second part of the protective liner is removed. The sticky side of the patch should not be touched. The patch

should be pressed down firmly with the palm of the hand for about 60 seconds, so that it sticks well.

Neupro does not need to be removed for bathing or swimming.

In the event that a patch becomes detached, a new patch should be applied for the remainder of the 24 hour dosing interval.

The patch should not be cut into pieces.

OVERDOSAGE

The most likely adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions and other signs of central dopaminergic stimulation.

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, the patch(es) should immediately be removed from the patient. Levels of rotigotine decrease after patch removal. Before stopping use of rotigotine completely see DOSAGE AND ADMINISTRATION – treatment discontinuation.

The patient should be monitored closely, including heart rate, heart rhythm and blood pressure. Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial.

Treatment of overdose may require general supportive measures to maintain the vital signs.

PRESENTATION AND STORAGE CONDITIONS

Thin, matrix type transdermal patch that is square shaped with rounded edges. The backing layer comprises a polyester film, siliconized, aluminized, colour coated with a tan coloured pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7). The protective liner comprises a transparent fluoropolymer coated polyester film. The outside of the tan coloured backing layer is imprinted with Neupro 1mg/24h, Neupro 2 mg/24 h, Neupro 3mg/24h, Neupro 4 mg/24 h, Neupro 6 mg/24 h or Neupro 8 mg/24 h respectively. Available in the following presentations:

Neupro 1 mg: 5 cm^2 patch containing 2.25 mg rotigotine with a nominal release rate of 1 mg rotigotine per 24 hours. Pack sizes: 7s, 28s, 100s
Neupro 2 mg: 10 cm^2 patch containing 4.5 mg rotigotine with a nominal release rate of 2 mg rotigotine per 24 hours. Pack sizes: 7s, 28s, 100s.
Neupro 3 mg: 15 cm^2 patch containing 6.75 mg rotigotine with a nominal release rate of 3 mg rotigotine per 24 hours. Pack sizes: 7s, 28s, 100s
Neupro 4 mg: 20 cm^2 patch containing 9.0 mg rotigotine with a nominal release rate of 4 mg rotigotine per 24 hours. Pack sizes 7s, 28s, 100s.
Neupro 6 mg: 30 cm^2 patch containing 13.5 mg rotigotine with a nominal release rate of 6 mg rotigotine per 24 hours. Pack sizes 7s, 28s, 100s.

Neupro 8 mg: 40 cm^2 patch containing 18.0 mg rotigotine with a nominal release rate of 8 mg rotigotine per 24 hours. Pack sizes 7s, 28s, 100s.

Each patch is individually sealed in a sachet.

Store at 2°C to 8°C (Refrigerate, Do not freeze).

NAME AND ADDRESS OF THE SPONSOR

UCB Pharma
A division of UCB Australia Pty Ltd
Level 1, 1155 Malvern Road
Malvern VIC 3144, Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

DATE OF APPROVAL

Date of TGA approval: 8th October 2010

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au