Rotigotine patches (Neupro) in early Parkinson's disease

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SYNTHETIC DRUG PROFILE

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder secondary to the progressive loss of dopaminergic neurons in the substantia nigra (a portion of the midbrain responsible for movement initiation and coordination) and appearance of bradykinesia, resting tremor, rigidity and postural reflex impairment. The most common symptomatic therapy is levodopa, a dopamine precursor; however, long-term treatment leads to involuntary movements and response fluctuations which add to the complexities of later disease-management. Monotherapy with dopamine agonists may represent an alternative approach with a reduced likelihood of motor complications; these drugs, initially introduced as adjunctive therapy to levodopa, are less effective in controlling motor disability and tend to cause more side effects than levodopa itself.

INDICATIONS AND DOSING

Rotigotine is a new chemical substance belonging to the group of non-ergolinic dopamine agonists. This drug is used for the treatment of early-stage Parkinson disease as monotherapy, or with levodopa at all stages of the disease. The drug is available in transdermal patches of several sizes, containing different doses of rotigotine (Table I).

Recently, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA issued a positive opinion on marketing authorization for rotigotine for idiopathic Restless Legs Syndrome (RLS) treatment. Rotigotine is currently included by AIFA (Agenzia Italiana del Farmaco) in a drug efficacy and safety monitoring program.

In early PD, the starting dose is 2mg/24h (4mg/24h for advanced PD), increased every week by 2mg/24h until an effective dose is reached, or up to a maximum dose of 8mg/24h (16mg/24h for advanced PD).

Size	10 cm^2	20 cm^2	30 cm^2	40 cm^2
Dose contained (mg)	4.5	9.0	13.5	18.0
Dose released (mg)	2	4	6	8

Table I

All available presentations for rotigotine transdermal application

PHARMACOKINETICS

The drug in the patch is constantly and dose-proportionately released over 24-h, resulting in constant plasmatic concentrations with daily application. The absorption of rotigotine is not influenced by gender, age, race, impaired renal or hepatic function. Rotigotine is widely distributed into tissues and extensively metabolized; the drug and its metabolites are mainly excreted in urine and less in bile and stool.

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Absorption	Bioavailability*	High variability (1- 64%), mean 37%
	Cmax	7 ng/ml after 1mg/Kg administration
	Tmax	15-18 h (1- 27 h)
	Binding to plasma proteins	90.5-92.7%
Metabolism and distribution	Volume of distribution	84 l/kg
	Metabolism	Dealkyilation/ monoidroxilation, conjugation with glucuronic or sulphate acid
	Enzimes	CYP450: CYP2C19 Several sulphotransferases and UDP-glucorosyltransferases
	Biological activity of metabolites	Not present
Elimination	Clearance	630 l/h
	Plasma terminal half-life	5-7 h
	Elimination	71% urine, 23% bile and faeces
	Interactions	No interactions

Table II
Absorption, distribution, metabolism and elimination of rotigotine after transdermal administration

FARMACODYNAMICS

Rotigotine acts like a typical dopamine-agonist: this drug shows a close structural and functional analogy to dopamine, with a similar receptor binding and functional profile. Rotigotine is an agonist at all dopamine receptors, showing highest affinity and activity via the D3 receptor (the most widely cited receptor in the inhibition of locomotor activity).

EFFICACY AND SAFETY

The clinical development program for the rotigotine patch comprised four main studies (Phase III trials): SP512 and SP513 to evaluate rotigotine efficacy in monotherapy in early-stage idiopathic PD; SP650 and SP515 to evaluate rotigotine efficacy in combination with levodopa in advanced idiopathic PD. SP512 and SP650 trials were placebo-controlled, whereas SP513 and SP515 were controlled against another dopamine agonist (ropinirole and pramipexole, respectively).

The primary efficacy end-point for monotherapy trials was based upon the UPDRS II/III score (Unified Parkinson's disease rating scale, a compilation of various PD assessment scales, the most frequently used for evaluating treatment responses), whereas for the evaluation of rotigotine in combination with levodopa the primary variable was the change in absolute time spent "off" (time during which PD symptoms are most prominent).

The safety profile of rotigotine can be considered typical of a dopamine-agonistic agent, with adverse reactions (AEs) like nausea, somnolence, vomiting, fatigue and constipation; the only exception is the high frequency of skin reactions in the application site. An increased frequency of AEs was observed in adjuvant therapy with levodopa, as compared to monotherapy.

Study	Design	Comparator	Efficacy	Safety
Monotherapy				
SP512	277 pts with early PD randomized 1:1 Double-blind, multi center, placebo-controlled	Placebo	**20% Improvement** P: 19% pts Rt: 48% pts ($p < 0.0001$) **Change in UPDRS II/III* score** P: 1.31 Rt: -3.98 ($p < 0.0001$)	AEs ≥ 5% subjects: P: 57% pz Rt: 76% pz Rp: 70% pz AEs typical of a dopamine agonist, with an higher frequency of skin reaction in the application site (P = 14%, Rt = 37%, Rp = 8%)
SP513	561 pts with early PD randomized 1:1:1 Double-blind, multi center, placebo-controlled, active treatment	Placebo, ropinirole	**20% Improvement** P: 30% pts Rt: 52% pts ($p < 0.0001$) Rp: 70% pts ($p < 0.0001$) **Change in UPDRS II/III* score** P: - 2.33 Rt: -6.83 Rp: -10.78 Not showed non-inferiority to Rp	

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Study	Design	Comparator	Efficacy	Safety
Adjoint to levodopa				
SP650	351 pts with advanced PD (≥ 2.5 h "OFF"/day) non adequately controlled by levodopa, randomized 1:1:1 Double-blind, placebo-controlled	Placebo	**Reduction in "off" time ≥ 30%** P: 34.5% Rt 18mg: 56.6% ($p < 0.001$) Rt 27mg: 55.1% ($p < 0.001$) **Change in "off" time (hrs)** P: 0.9 Rt 18mg: 2.7 ($p < 0.001$) Rt 27mg: 2.1 ($p = 0.003$)	AEs ≥ 5% subjects: P: 62.6% pz Rt: 73.0% pz Rp: 70.3 % pz AEs typical of a dopamine agonist, with an higher frequency of skin reaction in the application site (P: 20.1%, Rt: 39.9%, Pr: 11.9%)
SP515	506 pts with advanced PD (≥ 2.5 h "OFF"/day) non adequately controlled by levodopa, randomized 2:2:1 Double-blind, placebo-controlled.	Placebo, pramipexole	**Reduction in "off" time ≥ 30%** Pr: 35% Rt: 59.7% ($p < 0.001$) P: 67% ($p < 0.001$) **Change in "off" time (hrs)** P: 0.88 Rt: 2.46 ($p < 0.0001$) Pr: 2.81 ($p < 0.0001$) Showed non-inferiority to Pr	

Table III

Summary of main studies investigating efficacy and safety of rotigotine monotherapy for early PD (SP512, versus placebo; SP513, versus placebo and ropinirole) or for advanced PD, in combination with levodopa (SP650, versus placebo; SP515, versus placebo and pramipexole)

* UPDRS score (Unified Parkinson's disease rating scale) in part II (daily activities) and III (motor evaluations) of questionnaire is the primary efficacy end-point for monotherapy trials; maximum score is 160 (52 + 108) points (worst scenario) and the absence of disease signs is associated with a 0 score

AEs = adverse events ; P = placebo; Pr = pramipexole; Rp = ropinirole; Rt = rotigotine

ECONOMIC EVALUATIONS

We were not able to retrieve any published economic evaluation on the use of rotigotine in Parkinson disease.

In table IV we calculated monthly pharmaceutical costs for available therapies for PD treatment. For each formulation we valorized minimum and maximum dosing (from the Summary Product Characteristics - SPCs) and DDD (Defined Daily Dose) for one month of therapy, using retail price. For packages with identical price we considered the less costly one. This is not to be intended as a cost-minimization analysis, but as a simple overlook of currently available treatments.

Drug and dosing range			Reimbursed price / package	Price of therapy (1 month)		
Category	Active principle (DDD)			<	>	DDD
Anticholinergics	biperidene (10 mg)	2 mg	4.29	3.2175	21.45	10.725
		4 mg	5.33	3.198	9.594	7.995
		5 mg	2.94	35.28	70.56	35.28
Antihistaminics	orfenadrine (200 mg)	50 mg	2.12	2.544	10.176	5.088
Levodopa and derivates	levodopa + benserazide (600 mg)	100+25 mg	4.71	-	-	28.26
		200+50 mg	16.84	-	-	30.312
	s.r.	100+25 mg	5.56	-	-	33.36
	levodopa + carbidopa (600 mg)	100+25 mg	4.98	8.964	23.904	17.928
		250+25 mg	6.68	2.004	32.064	9.6192
	s.r.	100+25 mg	8.12	9.744	43.848	29.232
	s.r.	200+50 mg	9.93	19.86	79.44	29.79
	m.r.	100+25 mg	9.21	11.052	44.208	33.156
	m.r.	200+50 mg	11.01	22.02	33.03	33.03
	melevodopa + carbidopa (600 mg)	100 mg	9.12	27.36	54.72	54.72
		125 mg	9.12	9.12	54.72	43.776
		250 mg	9.12	9.12	54.72	21.888

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Drug and dosing range			Reimbursed price / package	Price of therapy (1 month)		
Category	Active principle (DDD)			<	>	DDD
Admantane derivates	amantadine (200 mg)*	100 mg	7.1	10.65	21.3	21.3
Dopamine agonists non ergot derived	apomorphine	30 mg	21.67	65.01	650.1	-
		50 mg**	39.402268	118.2	472.8	-
	rotigotine (6 mg)	2 mg	96.04	102.9	102.9	308.7
		4 mg	100.36	107.5286	107.5286	161.2929
		6 mg	130.47	139.7893	139.7893	139.7893
		8 mg	160.56	172.0286	172.0286	129.0214
	ropinirole (6 mg)	0.25 mg	4.75	40.71429	244.2857	162.8571
		0.5 mg	8.68	37.2	223.2	148.8
		1 mg	10.44	22.37143	134.2286	89.48571
		2 mg	20.82	29.74286	118.9714	89.22857
		5 mg	44.04	31.45714	125.8286	75.49714
	pramipexole (2.5 mg)	0.25 mg	16.52	33.04	297.36	165.2
		1 mg	65.16	65.16	293.22	162.9
Dopamine agonists ergot derived	cabergoline (3 mg)	1 mg	19.16	28.74	172.44	86.22
		2 mg	38.02	28.515	171.09	85.545
	bromocriptine (40 mg)	5 mg	11.53	11.53	46.12	92.24
		10 mg	14.66	10.995	43.98	87.96
	pergolide (3 mg)	0.05 mg	8.63	8.63	172.6	517.8
		0.25 mg	16.48	12.36	247.2	148.32
		1 mg	18.2	27.3	136.5	81.9
	dihydroergocryptine (60 mg)*	20 mg	34.88	26.16	313.92	156.96
MAO B inhibitors	selegiline (5 mg)*	1.25 mg	40.56	40.56	40.56	162.24
		5 mg	17.04	10.224	20.448	10.224
		10 mg	18.36	11.016	22.032	11.016
	rasagiline (1 mg)	1 mg	135.55	145.2321	145.2321	145.2321
Other dopaminergic substances	tolcapone (450 mg)	100 mg	165.33	148.797	297.594	223.1955
	entacapone (1 g)	200 mg	116.02	34.806	348.06	174.03

Table IV

Monthly pharmaceutical costs for different available therapies for PD treatment (Informatore Farmaceutico 2008)

* Not in the Italian reimbursement list; **Ex-factory price

PRODUCT OVERVIEW
Name of the Medicinal Product Neupro
Marketing Authorisation Holder SCHWARZ PHARMA Ltd
Active Substance Rotigotine
Pharmaco-therapeutic Group Dopamine agonist
ATC Code N04BC09
Date of issue of Marketing Authorisation valid throughout the European Union 15 February 2006

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