Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rivastigmine Orion 6 mg capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate equivalent to 6.0 mg, rivastigmine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Off-white to slightly yellow powder in a hard gelatin capsule with opaque red cap and opaque orange body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer’s dementia or dementia associated with Parkinson’s disease. Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor medicinal product intake by the patient.

Rivastigmine should be administered twice a day, with morning and evening meals. The capsules should be swallowed whole.

Initial dose: 1.5 mg twice a day.

Dose titration: The starting dose is 1.5 mg twice a day. If this dose is well tolerated after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks of treatment at that dose level.

If adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson’s disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued.

Maintenance dose: The effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose. The recommended maximum daily dose is 6 mg twice a day.

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. If after 3 months of maintenance dose treatment the patient's rate of decline in dementia symptoms is not altered favourably, the treatment should be discontinued. Discontinuation should also be considered when evidence of a therapeutic effect is no longer present.

Individual response to rivastigmine cannot be predicted. However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a larger effect was observed in Parkinson's disease patients with visual hallucinations (see section 5.1).

Treatment effect has not been studied in placebo-controlled trials beyond 6 months.

Re-initiation of therapy: If treatment is interrupted for more than several days, it should be re-initiated at 1.5 mg twice daily. Dose titration should then be carried out as described above.

Renal and hepatic impairment:
Due to increased exposure in renal and mild to moderate hepatic impairment, dosing recommendations to titrate according to individual tolerability should be closely followed (see section 5.2).

Patients with severe liver impairment have not been studied (see section 4.3).

Children: Rivastigmine is not recommended for use in children or adolescents (age below 18 years).

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with

- hypersensitivity to rivastigmine, other carbamate derivatives or to any of the excipients used in the formulation
- severe liver impairment, as it has not been studied in this population.

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with higher doses. If treatment is interrupted for more than several days, it should be re-initiated at 1.5 mg twice daily to reduce the possibility of adverse reactions (e.g. vomiting).

Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Rivastigmin Orion has been discontinued (see section 4.8).

Gastrointestinal disorders such as nausea and vomiting may occur particularly when initiating treatment and/or increasing the dose. These adverse reactions occur more commonly in women. Patients with Alzheimer's disease may lose weight. Cholinesterase inhibitors, including rivastigmine, have been associated with weight loss in these patients. During therapy patient's weight should be monitored.

In case of severe vomiting associated with rivastigmine treatment, appropriate dose adjustments as recommended in section 4.2 must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section 4.8). Such events appeared to occur particularly after dose increments or high doses of rivastigmine.

Care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section 4.8).

Rivastigmine may cause increased gastric acid secretions. Care should be exercised in treating patients with active gastric or duodenal ulcers or patients predisposed to these conditions.

Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

Cholinomimetics may induce or exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such diseases.

The use of rivastigmine in patients with severe dementia of Alzheimer's disease or associated with Parkinson's disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patients groups is not recommended.

Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson's disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and rivastigmine.

According to its metabolism, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

4.6 Fertility, pregnancy and lactation

Pregnancy:
For rivastigmine no clinical data on exposed pregnancies are available. No effects on fertility or embryofoetal development were observed in rats and rabbits, except at doses related to maternal toxicity. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

Lactation:
In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

4.7 Effects on ability to drive and use machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, rivastigmine can induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. Therefore, the ability of patients with dementia on rivastigmine to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

The most commonly reported adverse reactions are gastrointestinal, including nausea (38%) and vomiting (23%), especially during titration. Female patients in clinical studies were found to be more susceptible than male patients to gastrointestinal adverse reactions and weight loss.

The following adverse reactions, listed below in Table 1, have been accumulated in patients with Alzheimer's dementia treated with rivastigmine.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 1

Infections and infestations Very rare	 Urinary infection
Psychiatric disorders Common Common Uncommon Uncommon Very rare	 Agitation Confusion Insomnia Depression Hallucinations
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	 Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson´s disease)
Cardiac disorders Rare Very rare	 Angina pectoris Cardiac arrythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)
Vascular disorders Very rare	 Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	 Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Metabolism and nutritional disorders Very common	 Anorexia
Hepatobiliary disorders Uncommon	 Elevated liver function tests
Skin and subcutaneous tissue disorders Common Rare	 Sweating increased Rashes

General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Malaise
Uncommon	Accidental fall
Investigations	
Common	Weight loss

Table 2 shows the adverse reactions reported in patients with dementia associated with Parkinson's disease treated with rivastigmine.

Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
Nervous system disorders	
Very common	Tremor
Common	Dizziness
Common	Somnolence
Common	Headache
Common	Worsening of Parkinson's disease
Common	Bradykinesia
Common	Dyskinesia
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial Fibrillation
Uncommon	Atrioventricular block
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Skin and subcutaneous tissue disorders	
Common	Sweating increased
Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
Metabolism and nutritional disorders	
Common	Anorexia
Common	Dehydration
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Gait abnormality

Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with rivastigmine in patients with dementia associated with Parkinson´s disease with predeficed events that may reflect worsening of parkinsonian symptoms.

Table 3

Pre-defined adverse events that may reflect worsening of parkinsonian symptoms in patients with dementia associated with Parkinson's disease	**Originator of rivastigmine n (%)**	**Placebo n (%)**
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AE(s)	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson's disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)
Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

4.9 Overdose

Symptoms:
Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours.

Treatment:
As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse reactions should be given as necessary.

In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anticholinesterases, ATC code: N06D A03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3 mg dose decreases acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's disease, inhibition of AChE in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by rivastigmine was similar to that of AChE.

Clinical studies in Alzheimer's dementia (with the originator of rivastigmine)

The efficacy of rivastigmine has been established through the use of three independent, domain specific, assessment tools which were assessed at periodic intervals during 6 month treatment periods. These include the ADAS-Cog (a performance based measure of cognition), the CIBIC-Plus (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities relating to finances, etc.).

The patients studied had an MMSE (Mini-Mental State Examination) score of 10–24.

The results for clinically relevant responders pooled from two flexible dose studies out of the three pivotal 26-week multicentre studies in patients with mild-to-moderately severe Alzheimer's Dementia, are provided in Table 4 below. Clinically relevant improvement in these studies was defined a priori as at least 4-point improvement on the ADAS-Cog, improvement on the CIBIC-Plus, or at least a 10% improvement on the PDS.

In addition, a post-hoc definition of response is provided in the same table. The secondary definition of response required a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6–12 mg group, corresponding to this definition, was 9.3 mg. It is important to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

Table 4

	Patients with Clinically Significant Response (%)			
	Intent to Treat		**Last Observation Carried Forward**	
Response Measure	**Rivastigmine 6–12 mg N=473**	**Placebo N=472**	**Rivastigmine 6–12 mg N=379**	**Placebo N=444**
ADAS-Cog: improvement of at least 4 points	21***	12	25***	12
CIBIC-Plus: improvement	29***	18	32***	19
PDS: improvement of at least 10%	26***	17	30***	18
At least 4 points improvement on ADASCog with no worsening on CIBIC-Plus and PDS	10*	6	12**	6

*p<0.05, **p<0.01, ***p<0.001

Clinical studies in dementia associated with Parkinson's disease (with the originator of rivastigmine)

The efficacy of rivastigmine in dementia associated with Parkinson's disease has been demonstrated in a 24-week multicentre, double-blind, placebo-controlled core study and its 24-week open-label extension phase. Patients involved in this study had an MMSE (Mini-Mental State Examination) score of 10–24. Efficacy has been established by the use of two independent scales which were assessed at regular intervals during a 6-month treatment period as shown in Table 5 below: the ADAS-Cog, a measure of cognition, and the global measure ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change).

Table 5

Dementia associated with Parkinson's Disease	**ADAS-Cog** ***Rivastigmine***	**ADAS-Cog Placebo**	**ADCSCGIC** ***Rivastigmine***	**ADCS-CGIC Placebo**
ITT + RDO population	(n=329)	(n=161)	(n=329)	(n=165)
Mean baseline ±SD	23.8 ± 10.2	24.3 ± 10.5	n/a	n/a
Mean change at 24 weeks ± SD	**2.1 ± 8.2**	-0.7 ± 7.5	**3.8 ± 1.4**	4.3 ± 1.5
Adjusted treatment difference p-value versus placebo	2.88 <0.001[1]		n/a 0.007[2]	
ITT + LOCF population	(n=287)	(n=154)	(n=289)	(n=158)
Mean baseline ±SD	24.0 ± 10.3	24.5 ± 10.6	n/a	n/a
Mean change at 24 weeks ± SD	**2.5 ± 8.4**	-0.8 ± 7.5	**3.7 ± 1.4**	4.3=1.5
Adjusted treatment difference p-value versus placebo	3.54[1] <0.001[1]		n/a <0.001[2]	

[1] Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.

[2] Mean data shown for convenience, categorical analysis performed using van Elteren test
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs; LOCF: Last Observation Carried Forward

Although a treatment effect was demonstrated in the overall study population, the data suggested that a larger treatment effect relative to placebo was seen in the subgroup of patients with moderate dementia associated with Parkinson's disease. Similarly a larger treatment effect was observed in those patients with visual hallucinations (see Table 6).

Table 6

Dementia associated with Parkinson's Disease	**ADAS-Cog** ***Rivastigmine***	**ADAS-Cog Placebo**	**ADAS-Cog** ***Rivastigmine***	**ADAS-Cog Placebo**
	Patients with visual hallucinations		**Patients without visual hallucinations**	
ITT + RDO population	(n=107)	(n=60)	(n=220)	(n=101)
Mean baseline ± SD	25.4 ± 9.9	27.4 ± 10.4	23.1 ± 10.4	22.5 ± 10.1
Mean change at 24 weeks± SD	**1.0 ± 9.2**	-2.1 ± 8.3	**2.6 ± 7.6**	0.1 ± 6.9
Adjusted treatment difference p-value versus placebo	4.27[1] 0.002[1]		2.09[1] 0.015[1]	
	Patients with moderate dementia (MMSE 10-17)		**Patients with mild dementia (MMSE 18-24)**	
ITT + RDO population	(n=87)	(n=44)	(n=237)	(n=115)
Mean baseline ± SD	32.6 ± 10.4	33.7 ± 10.3	20.6 ± 7.9	20.7 ± 7.9
Mean change at 24 weeks± SD	**2.6 ± 9.4**	-1.8 ± 7.2	**1.9 ± 7.7**	-0.2 ± 7.5
Adjusted treatment difference p-value versus placebo	4.73[1] 0.002[1]		2.14[1] 0.010[1]	

[1] Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs.

5.2 Pharmacokinetic properties

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of the drug's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36%±13%. Administration of rivastigmine with food delays absorption (tmax) by 90 min and lowers Cmax and increases AUC by approximately 30%.

Distribution: Protein binding of rivastigmine is approximately 40%. It readily crosses the blood brain barrier and has an apparent volume of distribution in the range of 1.8–2.7 l/kg.

Metabolism: Rivastigmine is rapidly and extensively metabolised (half-life in plasma approximately 1 hour), primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. In vitro, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from in vitro and animal studies the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 l/h after a 0.2 mg intravenous dose and decreased to 70 l/h after a 2.7 mg intravenous dose.

Excretion: Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of 14C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

Elderly subjects: While bioavailability of rivastigmine is greater in elderly than in young healthy volunteers, studies in Alzheimer patients aged between 50 and 92 years showed no change in bioavailability with age.

Subjects with hepatic impairment: The C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Subjects with renal impairment: C_{max} and AUC of rivastigmine were more than twice as high in subjects with moderate renal impairment compared with healthy subjects; however there were no changes in C_{max} and AUC of rivastigmine in subjects with severe renal impairment.

5.3 Preclinical safety data

Repeated-dose toxicity studies in rats, mice and dogs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. No safety margins to human exposure were achieved in the animal studies due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of in vitro and in vivo tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose 10^4 times the maximum clinical exposure. The *in vivo* micronucleus test was negative.

No evidence of carcinogenicity was found in studies in mice and rats at the maximum tolerated dose, although the exposure to rivastigmine and its metabolites was lower than the human exposure. When normalised to body surface area, the exposure to rivastigmine and its metabolites was approximately equivalent to the maximum recommended human dose of 12 mg/day; however, when compared to the maximum human dose, a multiple of approximately 6-fold was achieved in animals.

In animals, rivastigmine crosses the placenta and is excreted into milk. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Magnesium stearate
Hypromellose
Cellulose, microcrystalline
Silica, colloidal anhydrous

Capsule shell:
Gelatin
Sodium laurilsulfate
Yellow iron oxide (E172)
Titanium dioxide (E171)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

PVC/PVdC/Aluminium blisters. Pack-sizes of 28, 56 and 112 capsules, hard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
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FIN-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA1327/13/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 2009

10 DATE OF REVISION OF THE TEXT