1. NAME OF THE MEDICINAL PRODUCT

Stalevo 50 mg/12.5 mg/200 mg film-coated tablets
Stalevo 75 mg/18.75 mg/200 mg film-coated tablets
Stalevo 100 mg/25 mg/200 mg film-coated tablets
Stalevo 125 mg/31.25 mg/200 mg film-coated tablets
Stalevo 150 mg/37.5 mg/200 mg film-coated tablets
Stalevo 175 mg/43.75 mg/200 mg film-coated tablets
Stalevo 200 mg/50 mg/200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg/12.5 mg/200 mg
Each tablet contains 50 mg of levodopa, 12.5 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 1.2 mg of sucrose.

75 mg/18.75 mg/200 mg
Each tablet contains 75 mg of levodopa, 18.75 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 1.4 mg of sucrose.

100 mg/25 mg/200 mg
Each tablet contains 100 mg of levodopa, 25 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 1.6 mg of sucrose.

125 mg/31.25 mg/200 mg
Each tablet contains 125 mg of levodopa, 31.25 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 1.6 mg of sucrose.

150 mg/37.5 mg/200 mg
Each tablet contains 150 mg of levodopa, 37.5 mg of carbidopa and 200 mg of entacapone.

Excipients with known effect:
Each tablet contains 1.9 mg of sucrose and 2.6 mg sodium as a constituent of an excipient.

175 mg/43.75 mg/200 mg
Each tablet contains 175 mg of levodopa, 43.75 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 1.89 mg of sucrose.

200 mg/50 mg/200 mg
Each tablet contains 200 mg of levodopa, 50 mg of carbidopa and 200 mg of entacapone.

Excipient with known effect:
Each tablet contains 2.3 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

50 mg/12.5 mg/200 mg
Brownish or greyish red, round, convex, unscored film-coated tablets marked with “LCE 50” on one side.

75 mg/18.75 mg/200 mg
Light brownish red, oval film-coated tablets marked with “LCE 75” on one side.

100 mg/25 mg/200 mg
Brownish or greyish red, oval, unscored film-coated tablets marked with “LCE 100” on one side.

125 mg/31.25 mg/200 mg
Light brownish red, oval film-coated tablets marked with “LCE 125” on one side.

150 mg/37.5 mg/200 mg
Brownish or greyish red, elongated-ellipse shaped, unscored film-coated tablets marked with “LCE 150” on one side.

175 mg/43.75 mg/200 mg
Light brownish red, oval, unscored film-coated tablets marked with “LCE 175” on one side.

200 mg/50 mg/200 mg
Dark brownish red, oval, unscored film-coated tablets marked with “LCE 200” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Stalevo is indicated for the treatment of adult patients with Parkinson’s disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

4.2 Posology and method of administration

Posology

The optimum daily dose must be determined by careful titration of levodopa in each patient. The daily dose should be preferably optimised using one of the seven available tablet strengths (50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/200 mg or 200 mg/50 mg/200 mg levodopa/carbidopa/entacapone).

Patients should be instructed to take only one Stalevo tablet per dose administration. Patients receiving less than 70–100 mg carbidopa a day are more likely to experience nausea and vomiting. While the experience with total daily dose greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2 000 mg and therefore the maximum dose is 10 tablets per day for the Stalevo strengths of 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg and 150 mg/37.5 mg/200 mg. Ten tablets of Stalevo 150 mg/37.5 mg/200 mg equals 375 mg of carbidopa a day. According to this daily carbidopa dose, the maximum recommended daily dose of Stalevo 175 mg/43.75 mg/200 mg is 8 tablets per day and Stalevo 200 mg/50 mg/200 mg dose is 7 tablets per day.

Usually Stalevo is to be used in patients who are currently treated with corresponding doses of

standard release levodopa/DDC inhibitor and entacapone.

How to transfer patients taking levodopa/DDC inhibitor (carbidopa or benserazide) preparations and entacapone tablets to Stalevo

a. Patients who are currently treated with entacapone and with standard release levodopa/carbidopa in doses equal to Stalevo tablet strengths can be directly transferred to corresponding Stalevo tablets. For example, a patient taking one tablet of 50 mg/12.5 mg of levodopa/carbidopa with one tablet of entacapone 200 mg four times daily can take one 50 mg/12.5 mg/200 mg Stalevo tablet four times daily in place of their usual levodopa/carbidopa and entacapone doses.

b. When initiating Stalevo therapy for patients currently treated with entacapone and levodopa/carbidopa in doses not equal to Stalevo tablets (50 mg/12.5 mg/200 mg or 75 mg/18.75 mg/200 mg or 100 mg/25 mg/200 mg or 125 mg/31.25 mg/200 mg or 150 mg/37.5 mg/200 mg or 175 mg/43.75 mg/200 mg or 200 mg/50 mg/200 mg), Stalevo dosing should be carefully titrated for optimal clinical response. At the initiation, Stalevo should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.

c. When initiating Stalevo in patients currently treated with entacapone and levodopa/benserazide in a standard release formulation, the dosing of levodopa/benserazide should be discontinued in the previous night, and Stalevo should be started in the next morning. The starting dose of Stalevo should provide either the same amount of levodopa or slightly (5–10%) more.

How to transfer patients not currently treated with entacapone to Stalevo

Initiation of Stalevo may be considered at corresponding doses to current treatment in some patients with Parkinson's disease and end-of-dose motor fluctuations, who are not stabilised on their current standard release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Stalevo is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate treatment (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Stalevo.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dose by 10–30% within the first days to first weeks after initiating Stalevo treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

Dose adjustment during the course of the treatment

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Stalevo should be considered, within the dose recommendations.

When less levodopa is required, the total daily dose of Stalevo should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Stalevo at an administration.

If other levodopa products are used concomitantly with a Stalevo tablet, the maximum dose recommendations should be followed.

Discontinuation of Stalevo therapy: If Stalevo treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is transferred to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms.

Paediatric population: The safety and efficacy of Stalevo in children aged below 18 years have not been established. No data are available.

Elderly: No dose adjustment of Stalevo is required for elderly.

Hepatic impairment: It is advised that Stalevo should be administered cautiously to patients with mild to moderate hepatic impairment. Dose reduction may be needed (see section 5.2). For severe hepatic impairment see section 4.3.

Renal impairment: Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, therefore Stalevo therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapy (see section 5.2).

Method of administration
Each tablet is to be taken orally either with or without food (see section 5.2). One tablet contains one treatment dose and the tablet may only be administered as whole tablets.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe hepatic impairment.
- Narrow-angle glaucoma.
- Pheochromocytoma.
- Coadministration of Stalevo with non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).
- Coadministration with a selective MAO-A inhibitor and a selective MAO-B inhibitor (see section 4.5).
- A previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.

4.4 Special warnings and precautions for use

- Stalevo is not recommended for the treatment of drug-induced extrapyramidal reactions.
- Stalevo therapy should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease, history of peptic ulcer disease or history of convulsions.
- In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias; cardiac function should be monitored with particular care during the period of initial dose adjustments.
- All patients treated with Stalevo should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current psychosis should be treated with caution.
- Concomitant administration of antipsychotics with dopamine receptor-blocking properties, particularly D_2 receptor antagonists should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms.
- Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure.
- Stalevo may induce orthostatic hypotension. Therefore Stalevo should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.
- Entacapone in association with levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving or operating machines (see section 4.7).
- In clinical studies, dopaminergic adverse reactions, e.g. dyskinesia, were more common in patients who received entacapone and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to those who received placebo with this combination. The doses of other antiparkinsonian medicinal products may need to be adjusted when Stalevo treatment is substituted for a patient currently not treated with entacapone.
- Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has

been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dose reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. NMS, including rhabdomyolysis and hyperthermia, is characterised by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g., agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase. In individual cases, only some of these symptoms and/or findings may be evident. The early diagnosis is important for the appropriate management of NMS. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Neither NMS nor rhabdomyolysis have been reported in association with entacapone treatment from controlled trials in which entacapone was discontinued abruptly. Since the introduction of entacapone into the market, isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone and other concomitant dopaminergic medicinal products. When considered necessary, the replacement of Stalevo with levodopa and DDC inhibitor without entacapone or other dopaminergic treatment should proceed slowly and an increase in levodopa dose may be necessary.

- If general anaesthesia is required, therapy with Stalevo may be continued for as long as the patient is permitted to take fluids and medicinal products by mouth. If therapy has to be stopped temporarily, Stalevo may be restarted as soon as oral medicinal products can be taken at the same daily dose as before.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Stalevo.
- For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhoea appearing during use of entacapone may be a sign of colitis. In the event of prolonged or persistent diarrhoea, the drug should be discontinued and appropriate medical therapy and investigations considered.
- Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Stalevo. Review of treatment is recommended if such symptoms develop.
- Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).
- For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.
- Levodopa/carbidopa may cause false positive result when a dipstick is used to test for urinary ketone and this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glycosuria.
- Stalevo contains sucrose, and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Stalevo 150 mg/37.5 mg/200 mg contains 2.6 mg sodium per tablet. The maximum recommended daily dose (10 tablets) contains 26 mg sodium, equivalent to 1.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- Stalevo 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 175 mg/43.75 mg/200 mg and 200 mg/50 mg/200 mg film-coated tablets contain less than 1 mmol (23 mg) sodium per maximum recommended daily dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Other antiparkinsonian medicinal products: To date there has been no indication of interactions that

would preclude concurrent use of standard antiparkinsonian medicinal products with Stalevo therapy. Entacapone in high doses may affect the absorption of carbidopa. However, no interaction with carbidopa has been observed with the recommended treatment schedule (200 mg of entacapone up to 10 times daily). Interactions between entacapone and selegiline have been investigated in repeated dose studies in Parkinson's disease patients treated with levodopa/DDC inhibitor and no interaction was observed. When used with Stalevo, the daily dose of selegiline should not exceed 10 mg.

Caution should be exercised when the following active substances are administered concomitantly with levodopa therapy.

Antihypertensives: Symptomatic postural hypotension may occur when levodopa is added to the treatment of patients already receiving antihypertensives. Dose adjustment of the antihypertensive agent may be required.

Antidepressants: Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants and levodopa/carbidopa. Interactions between entacapone and imipramine and between entacapone and moclobemide have been investigated in single dose studies in healthy volunteers. No pharmacodynamic interactions were observed. A significant number of Parkinson's disease patients have been treated with the combination of levodopa, carbidopa and entacapone with several active substances including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine and medicinal products that are metabolised by COMT (e.g. catechol-structured compounds, paroxetine). No pharmacodynamic interactions have been observed. However, caution should be exercised when these medicinal products are used concomitantly with Stalevo (see sections 4.3 and 4.4).

Other active substances: Dopamine receptor antagonists (e.g. some antipsychotics and antiemetics), phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these medicinal products with Stalevo should be carefully observed for loss of therapeutic response.

Due to entacapone's affinity to cytochrome P450 2C9 *in vitro* (see section 5.2), Stalevo may potentially interfere with active substances whose metabolism is dependent on this isoenzyme, such as S-warfarin. However, in an interaction study with healthy volunteers, entacapone did not change the plasma levels of S-warfarin, while the AUC for R-warfarin increased on average by 18% [CI_{90} 11–26%]. The INR values increased on average by 13% [CI_{90} 6–19%]. Thus, a control of INR is recommended when Stalevo is initiated for patients receiving warfarin.

Other forms of interactions: Since levodopa competes with certain amino acids, the absorption of Stalevo may be impaired in some patients on high protein diet.

Levodopa and entacapone may form chelates with iron in the gastrointestinal tract. Therefore, Stalevo and iron preparations should be taken at least 2–3 hours apart (see section 4.8).

In vitro data: Entacapone binds to human albumin binding site II which also binds several other medicinal products, including diazepam and ibuprofen. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products. Accordingly, to date there has been no indication of such interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicity of the separate compounds (see section 5.3). The potential risk for humans is unknown. Stalevo should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus.

Breast-feeding
Levodopa is excreted in human breast milk. There is evidence that breast-feeding is suppressed during

treatment with levodopa. Carbidopa and entacapone were excreted in milk in animals but is not known whether they are excreted in human breast milk. The safety of levodopa, carbidopa or entacapone in the infant is not known. Women should not breast-feed during treatment with Stalevo.

Fertility
No adverse reactions on fertility were observed in preclinical studies with entacapone, carbidopa or levodopa alone. Fertility studies in animals have not been conducted with the combination of entacapone, levodopa and carbidopa.

4.7 Effects on ability to drive and use machines

Stalevo may have a major influence on the ability to drive and use machines. Levodopa, carbidopa and entacapone together may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

Patients being treated with Stalevo and presenting with somnolence and/or sudden sleep onset episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes have resolved (see section 4.4).

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions with Stalevo are dyskinesias occurring in approximately 19% of patients; gastrointestinal symptoms including nausea and diarrhoea occurring in approximately 15% and 12% of patients, respectively; muscle, musculoskeletal and connective tissue pain occurring in approximately 12% of patients; and harmless reddish-brown discolouration of urine (chromaturia) occurring in approximately 10% of patients. Serious events of gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been identified from the clinical trials with Stalevo or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur with Stalevo although no cases have been identified from the clinical trial data.

b. Tabulated list of adverse reactions

The following adverse reactions, listed in Table 1, have been accumulated both from a pooled data of eleven double-blind clinical trials consisting of 3 230 patients (1 810 treated with Stalevo or entacapone combined with levodopa/DDC inhibitor, and 1 420 treated with placebo combined with levodopa/DDC inhibitor or cabergoline combined with levodopa/ DDC inhibitor), and from the post-marketing data since the introduction of entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor.

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), not known (cannot be estimated from the available data, since no valid estimate can be derived from clinical trials or epidemiological studies).

Table 1. Adverse reactions

Blood and lymphatic system disorders
Common: Anaemia
Uncommon: Thrombocytopenia

Metabolism and nutrition disorders
Common: Weight decreased*, decreased appetite*

Psychiatric disorders

Common:	Depression, hallucination, confusional state*, abnormal dreams*, anxiety, insomnia
Uncommon:	Psychosis, agitation*
Not known:	Suicidal behaviour, Dopamine dysregulation syndrome

Nervous system disorders

Very common:	Dyskinesia*
Common:	Parkinsonism aggravated (e.g. bradykinesia)*, tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness*, headache
Not known:	Neuroleptic malignant syndrome*

Eye disorders

Common:	Blurred vision

Cardiac disorders

Common:	Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris)**, irregular heart rhythm
Uncommon:	Myocardial infarction**

Vascular disorders

Common:	Orthostatic hypotension, hypertension
Uncommon:	Gastrointestinal haemorrhage

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea

Gastrointestinal disorders

Very common:	Diarrhoea*, nausea*
Common:	Constipation*, vomiting*, dyspepsia, abdominal pain and discomfort*, dry mouth*
Uncommon:	Colitis*, dysphagia

Hepatobiliary disorders

Uncommon:	Hepatic function test abnormal*
Not known:	Hepatitis with mainly cholestatic features (see section 4.4)*

Skin and subcutaneous tissue disorders

Common:	Rash*, hyperhidrosis
Uncommon:	Discolourations other than urine (e.g. skin, nail, hair, sweat)*
Rare:	Angioedema
Not known:	Urticaria*

Musculoskeletal and connective tissue disorders

Very common:	Muscle, musculoskeletal and connective tissue pain*
Common:	Muscle spasms, arthralgia
Not known:	Rhabdomyolysis*

Renal and urinary disorders

Very common:	Chromaturia*
Common:	Urinary tract infection
Uncommon:	Urinary retention

General disorders and administration site conditions

Common:	Chest pain, peripheral oedema, fall, gait disturbance, asthenia, fatigue
Uncommon:	Malaise

*Adverse reactions that are mainly attributable to entacapone or are more frequent (by the frequency difference of at least 1% in the clinical trial data) with entacapone than levodopa/DDC inhibitor alone. See section c.

**The incidence rates of myocardial infarction and other ischemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2 082 patients with end-of-dose motor fluctuations receiving entacapone.

c. Description of selected adverse reactions

Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk in Table 1, section 4.8b. Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat. Other adverse reactions with an asterisk in Table 1, section 4.8b are marked based on either their more frequent occurring (by the frequency difference of at least 1%) in the clinical trial data with entacapone than levodopa/DDCI alone or the individual case safety reports received after the introduction of entacapone into the market.

Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa therapy has not been established.

Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Stalevo (see section 4.4).

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Entacapone in association with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The post-marketing data includes isolated cases of overdose in which the reported highest daily doses of levodopa and entacapone have been at least 10 000 mg and 40 000 mg, respectively. The acute symptoms and signs in these cases of overdose included agitation, confusional state, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration, discolourations of skin, tongue and conjunctiva, and chromaturia. Management of acute overdose with Stalevo therapy is similar to acute overdose with levodopa. Pyridoxine, however, is not effective in reversing the actions of Stalevo. Hospitalisation is advised and general supportive measures should be employed with immediate gastric lavage and repeated doses of charcoal over time. This may hasten the elimination of entacapone in particular by decreasing its absorption/reabsorption from the GI tract. The adequacy of the respiratory, circulatory and renal systems should be carefully monitored and appropriate

supportive measures employed. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmias. If required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient has taken other active substances in addition to Stalevo should be taken into consideration. The value of dialysis in the treatment of overdose is not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parkinson drugs, dopa and dopa derivatives, ATC code: N04BA03

According to the current understanding, the symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Dopamine does not cross the blood-brain barrier. Levodopa, the precursor of dopamine, crosses the blood brain barrier and relieves the symptoms of the disease. As levodopa is extensively metabolised in the periphery, only a small portion of a given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors.

Carbidopa and benserazide are peripheral DDC inhibitors which reduce the peripheral metabolism of levodopa to dopamine, and thus, more levodopa is available to the brain. When decarboxylation of levodopa is reduced with the co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse reactions such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, catechol-*O*-methyltransferase (COMT) becomes the major peripheral metabolic pathway catalyzing the conversion of levodopa to 3-O-methyldopa (3-OMD), a potentially harmful metabolite of levodopa. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased area under the curve (AUC) in the pharmacokinetic profile of levodopa. Consequently the clinical response to each dose of levodopa is enhanced and prolonged.

The evidence of the therapeutic effects of Stalevo is based on two phase III double-blind studies, in which 376 Parkinson's disease patients with end-of-dose motor fluctuations received either entacapone or placebo with each levodopa/DDC inhibitor dose. Daily ON time with and without entacapone was recorded in home-diaries by patients. In the first study, entacapone increased the mean daily ON time by 1 h 20 min (CI $_{95\%}$ 45 min, 1 h 56 min) from baseline. This corresponded to an 8.3% increase in the proportion of daily ON time. Correspondingly, the decrease in daily OFF time was 24% in the entacapone group and 0% in the placebo group. In the second study, the mean proportion of daily ON time increased by 4.5% (CI$_{95\%}$ 0.93%, 7.97%) from baseline. This is translated to a mean increase of 35 min in the daily ON time. Correspondingly, the daily OFF time decreased by 18% on entacapone and by 5% on placebo. Because the effects of Stalevo tablets are equivalent with entacapone 200 mg tablet administered concomitantly with the commercially available standard release carbidopa/levodopa preparations in corresponding doses these results are applicable to describe the effects of Stalevo as well.

5.2 Pharmacokinetic properties

General characteristics of the active substances

Absorption/distribution: There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone. Both levodopa and entacapone are rapidly absorbed and eliminated. Carbidopa is absorbed and eliminated slightly slower compared with levodopa. When given separately without the two other active substances, the bioavailability for levodopa is 15–33%, for carbidopa 40–70% and for entacapone 35% after a 200 mg oral dose. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone. The distribution volume of both levodopa (Vd 0.36–1.6 l/kg) and entacapone (Vd_{ss} 0.27 l/kg) is moderately small while no data for carbidopa are available.

Levodopa is bound to plasma protein only to a minor extent of about 10–30% and carbidopa is bound approximately 36%, while entacapone is extensively bound to plasma proteins (about 98%) – mainly to serum albumin. At therapeutic concentrations, entacapone does not displace other extensively bound active substances (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these substances at therapeutic or higher concentrations.

Biotransformation and elimination: Levodopa is extensively metabolised to various metabolites: decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT) being the most important pathways.

Carbidopa is metabolized to two main metabolites which are excreted in the urine as glucuronides and unconjugated compounds. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone is almost completely metabolized prior to excretion via urine (10 to 20%) and bile/faeces (80 to 90%). The main metabolic pathway is glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5% of plasma total amount.

Total clearance for levodopa is in the range of 0.55–1.38 l/kg/h and for entacapone is in the range of 0.70 l/kg/h. The elimination-half life is ($t_{1/2}$) is 0.6–1.3 hours for levodopa, 2–3 hours for carbidopa and 0.4–0.7 hours for entacapone, each given separately.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs on repeated administration.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19); see section 4.5.

Characteristics in patients

Elderly: When given without carbidopa and entacapone, the absorption of levodopa is greater and elimination is slower in elderly than in young people. However, after combination of carbidopa with levodopa, the absorption of levodopa is similar between the elderly and the young people, but the AUC is still 1.5 fold greater in the elderly due to decreased DDC activity and lower clearance by aging. There are no significant differences in the AUC of carbidopa or entacapone between younger (45–64 years) and elderly (65–75 years).

Gender: Bioavailability of levodopa is significantly higher in women than in men. In the pharmacokinetic studies with Stalevo the bioavailability of levodopa is higher in women than in men, primarily due to the difference in body weight, while there is no gender difference with carbidopa and entacapone.

Hepatic impairment: The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases (see sections 4.2 and 4.3). No particular studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment are reported, however, it is advised that Stalevo should be administered cautiously to patients with mild or moderate hepatic impairment.

Renal impairment: Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. However, a longer dosing interval of Stalevo may be considered for patients who are receiving dialysis therapy (see section 4.2).

5.3 Preclinical safety data

Preclinical data of levodopa, carbidopa and entacapone, tested alone or in combination, revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In repeated dose toxicity studies with entacapone, anaemia most likely due to iron chelating properties of entacapone was observed. Regarding reproduction toxicity of entacapone, decreased foetal weight and a slightly delayed bone development were noticed in rabbits treated at systemic exposure levels in the therapeutic range. Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Magnesium stearate
Maize starch
Mannitol (E421)
Povidone K 30 (E1201)

Film-coating of 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 mg:
Glycerol (85 per cent) (E422)
Hypromellose
Magnesium stearate
Polysorbate 80
Red iron oxide (E172)
Sucrose
Titanium dioxide (E171)
Yellow iron oxide (E172)

Film-coating of 75/18.75/200 mg, 125/31.25/200 mg, 175/43.75/200 mg and 200/50/200 mg:
Glycerol (85 per cent) (E422)
Hypromellose
Magnesium stearate
Polysorbate 80
Red iron oxide (E172)
Sucrose
Titanium dioxide (E171)

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 conditions.

6.5 Nature and contents of container

HDPE bottle with a child resistant PP-closure.

Pack sizes of 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 mg:

10, 30, 100, 130, 175 and 250 tablets.

Pack sizes of 75/18.75/200 mg, 125/31.25/200 mg, 175/43.75/200 mg and 200/50/200 mg:
10, 30, 100, 130 and 175 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBERS

50 mg/12.5 mg/200 mg
EU/1/03/260/001-004
EU/1/03/260/013
EU/1/03/260/016

75 mg/18.75 mg/200 mg
EU/1/03/260/024-028

100 mg/25 mg/200 mg
EU/1/03/260/005-008
EU/1/03/260/014
EU/1/03/260/017

125 mg/31.25 mg/200 mg
EU/1/03/260/029-033

150 mg/37.5 mg/200 mg
EU/1/03/260/009-012
EU/1/03/260/015
EU/1/03/260/018

175 mg/43.75 mg/200 mg
EU/1/03/260/034-038

200 mg/50 mg/200 mg
EU/1/03/260/019-023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 October 2003
Date of latest renewal: 17 October 2008

10. DATE OF REVISION OF THE TEXT

27th January 2022

Detailed information on this medicinal product is available on the website of European Medicines Agency http://www.ema.europa.eu.