NOVARTIS

NAME OF THE MEDICINAL PRODUCT

Stalevo®

COMPOSITION AND PHARMACEUTICAL FORM

Stalevo 50 mg/12.5 mg/200 mg each tablet contains 50 mg of levodopa, 12.5 mg of carbidopa and 200 mg of entacapone. They are brownish- or greyish-red, round, convex, unscored film-coated tablets marked with 'LCE 50' on one side.

Stalevo 100 mg/25 mg/200 mg each tablet contains 100 mg of levodopa, 25 mg of carbidopa and 200 mg of entacapone. They brownish- or greyish-red, oval-shaped, unscored film-coated tablets marked with 'LCE 100' on one side.

Stalevo 150 mg/37.5 mg/200 mg each tablet contains 150 mg of levodopa, 37.5 mg of carbidopa and 200 mg of entacapone. They are brownish- or greyish-red, elongated-ellipse shaped unscored film-coated tablets marked with 'LCE 150' on one side.

Stalevo 200 mg/50 mg/200 mg each tablet contains 200 mg of levodopa, 50 mg of carbidopa and 200 mg of entacapone. They are dark brownish- or greyish-red, oval-shaped unscored film coated tablets marked with 'LCE 200' on one side.

For a full list of excipients, see section LIST OF EXCIPIENTS. Certain dosage strengths may not be available in all countries.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

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

POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration

Each tablet is to be taken orally either with or without food (see section PHARMACOKINETICS PROPERTIES). One tablet contains one treatment dose. The tablets should always be swallowed whole.

The optimum daily dosage must be determined by careful titration of levodopa in each patient. The daily dose should preferably be optimised using one of the four available tablet strengths (50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg or 200/50/200mg 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 dosage greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2000 mg and therefore the

maximum Stalevo dose , for the Stalevo strengths of 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 mg, is 10 tablets per day. Ten (10) tablets of Stalevo 150/37.5/200 mg equals 375 mg of carbidopa a day. Therefore, using a maximum recommended daily dose of 375 mg of carbidopa, the maximum daily dose of Stalevo 200/50/200 mg is 7 tablets per day.

The maximum total daily levodopa dose administered in the form of Stalevo should not exceed 1500 mg.

Starting Stalevo therapy

Switching from levodopa/ DDC inhibitor (carbidopa or benserazide) preparations and entacapone to Stalevo

Usually Stalevo is intended for use in patients already receiving treatment with corresponding doses of standard-release levodopa/DDC inhibitor and entacapone.

As with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Stalevo. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Stalevo. Stalevo may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

a. Patients who are currently receiving treatment with entacapone and standard-release levodopa/carbidopa in doses equal to Stalevo tablet strengths can be directly switched to the corresponding Stalevo tablets, for example:

Levodopa/Carbidopa	Entacapone	Equivalent Stalevo
50/12.5 mg	200 mg	50/12.5/200 mg
100/25 mg	200 mg	100/25/200 mg
150/37.5 mg	200 mg	150/37.5/200 mg
200/50 mg	200 mg	200/50/200 mg

b. When initiating Stalevo therapy in patients currently receiving treatment with entacapone and levodopa/carbidopa in doses not equal to the available Stalevo tablet strengths (50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg or 200/50/200mg), Stalevo dosing should be carefully titrated for optimal clinical response. At the start of therapy, 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, treatment should be stopped for one night and Stalevo therapy started the next morning. The therapy should begin with a dosage of Stalevo that will provide either the same amount of levodopa or slightly (5-10%) more.

d. There are no data on transferring patients from controlled-release formulations or standard release preparations with a 10:1 ratio of levodopa/DDC inhibitor to Stalevo.

Switching in patients not currently treated with entacapone to Stalevo

As with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Stalevo. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Stalevo. Stalevo may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

Initiation of Stalevo at a dosage corresponding to current treatment may be considered 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 600 mg. In such patients it is advisable to introduce entacapone treatment as a separate medication (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 dosage 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.

Dosage 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 dosage recommendations.

When less levodopa is required, the total daily dosage 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 dosage recommendations should be followed.

Discontinuation of Stalevo therapy

If Stalevo treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is switched 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 (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE, rhabdomyolysis).

Children and adolescents

The safety and efficacy of Stalevo in children aged below 18 years have not been established.

No data are available. Stalevo is not recommended for use in children below age of 18.

Elderly

No adjustment of Stalevo dosage is necessary in elderly patients.

Renal impairment

Renal impairment does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment, and Stalevo should therefore be administered with caution in patients with severe renal impairment including those receiving dialysis therapy (see section PHARMACOKINETICS PROPERTIES).

CONTRAINDICATIONS

- Known hypersensitivity to the active substances or to any of the excipients.
- Liver impairment.
- Narrow-angle glaucoma.
- Pheochromocytoma.
- Co-administrationof a non-selective monoamine oxidase (MAO-A and MAO-B) inhibitor (e.g. phenelzine, tranylcypromine).
- Co-administration use of a selective MAO-A inhibitor and a selective MAO-B inhibitor (see section INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS, other antiparkinsonian medicinal products). These inhibitors must be discontinued at least two weeks prior to initiating therapy with Stalevo.
- A history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.
- Because levodopa may activate malignant melanoma, Stalevo should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Stalevo is not recommended for the treatment of drug-induced extrapyramidal reactions.

Stalevo therapy should be administered with caution to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease, or history of peptic ulcer disease or 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 dosage adjustments.

All patients treated with Stalevo should be monitored carefully for the development of mental changes (e.g. hallucinoses and psychoses), depression with suicidal tendencies, and 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 caution is necessary when giving Stalevo to patients who are taking other medicinal products which may cause orthostatic hypotension.

Entacapone in combination 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 also section EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

In clinical studies, undesirable dopaminergic effects, 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 is introduced in a patient not previously treated with entacapone.

Rhabdomyolysis secondary to severe dyskinesias or Neuroleptic Malignant Syndrome (NMS) has been observed rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment. 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. Early diagnosis is important for the appropriate management of NMS. A syndrome resembling NMS including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone.

When considered necessary, withdrawal of Stalevo and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of Stalevo, an increase in levodopa dosage may be necessary.

Prescribers should exercise caution when switching patients from Stalevo to levodopa/DDC inhibitor therapy without entacapone. When considered necessary, the replacement of Stalevo with levodopa and DDC inhibitor without entacapone should proceed slowly and an increase in levodopa dosage 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 medication by mouth. If therapy has to be stopped temporarily, Stalevo may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Stalevo.

For patients experiencing diarrhea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhea suspected to be related to Stalevo may be a sign of colitis. In the event of prolonged or persistent diarrhea, the drug should be discontinued and appropriate medical therapy and investigations considered.

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.

Dopamine dysregulation syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see section UNDESIRABLE EFFECTS).

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers 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 developLevodopa/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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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.

Because Stalevo contains entacapone, it should not be used concurrently with Comtan (entacapone).

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

Antihypertensives

Symptomatic postural hypotension may occur when levodopa is initiated in patients already receiving antihypertensives. Dosage 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: rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine, and paroxetine). No pharmacodynamic interactions have been observed. However, caution should be exercised when these medicinal products are used concomitantly with Stalevo (see also section CONTRAINDICATIONS and section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 PHARMACOKINETICS PROPERTIES), 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 in 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 a 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 UNDESIRABLE EFFECTS).

Stalevo may be given to patients with Parkinson's disease who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

Because of its mechanism of action, entacapone may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with medicinal products metabolized by catechol-O-methyl transferase (COMT), e.g. rimiterol, isoprenaline, adrenaline, noradrenalin, dopamine, dobutamine, alpha-methyldopa apomorphine.

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.

PREGNANCY AND BREAST-FEEDING

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 PRECLINICAL SAFETY DATA). The potential risk for humans is unknown. Stalevo should not be used during pregnancy.

Breast-feeding

Levodopa is excreted in human breast milk. There is evidence that lactation is suppressed during treatment with levodopa. Carbidopa and entacapone were excreted in milk in animals but it 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Stalevo may have a major influence on the ability to drive and use 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 also section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Levodopa, carbidopa and entacapone together may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

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 diarrhea 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 3230 patients (1810 treated with Stalevo or entacapone combined with levodopa/DDC inhibitor, and 1420 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, delusions, euphoria, 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
Rare:	Paraesthesia
Not known:	Neuroleptic malignant syndrome*, ataxia, numbness, bitter taste
Eye disorders	
Common:	Blurred vision
Not known:	Diplopia
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
Rare:	Phlebitis
Not known:	Flushing, hot flush
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea
Not known:	Hiccups, dysphonia
Gastrointestinal disorders	
Very common:	Diarrhoea*, nausea*
Common:	Constipation*, vomiting*, dyspepsia, abdominal pain and discomfort*, dry mouth*
Uncommon:	Colitis*, dysphagia
Rare:	Development of duodenal ulcer
Not known:	Salivary hypersecretion, bruxism, flatulence, glossodynia
Hepatobiliary disorders	
Uncommon:	Hepatic function test abnormal*
Not known:	Hepatitis with mainly cholestatic features (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE)*
Skin and subcutaneous tissue disorders	
Common:	Rash*, hyperhidrosis
Uncommon:	Discolourations other than urine (e.g. skin, nail, hair, sweat)*
Rare:	Angioedema
Not known:	Urticaria*, alopecia
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 2082 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 diarrhea 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 occurrence (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.

Dopamine dysregulation syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/carbidopa. 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 section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Entacapone in association with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes.

Laboratory tests

The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and should, therefore, be borne in mind when treating patients with Stalevo:

Transient abnormalities include elevated values of blood urea.

Elevated serum glucose and blood in the urine have been reported.

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 overdosage with Stalevo is similar to acute overdosage with levodopa. 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 gastrointestinal 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 overdosage is not known.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-parkinsonian dopaminergic medicinal product (ATC code: N04B A03).According to 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, resulting in an increase in the amount of levodopa 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 the inhibition of the decarboxylase by a DDC inhibitor, 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, 1h 56min) 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.

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 more slowly than levodopa. When given separately without the other two active substances, the bioavailability of levodopa is 15-33%, that of carbidopa 40-70% and that of 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; no data are available for carbidopa.

Levodopa is bound to plasma proteins only to a minor extent (about 10-30%), while carbidopa is bound approximately 36%, and while entacapone is extensively bound (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.

Metabolism 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 metabolised 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 metabolised 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 the total amount in plasma.

Total clearance of levodopa is in the range of 0.55-1.38 L/kg/h and that of 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 h 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 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS).

Characteristics in patients

Elderly

In elderly patients given levodopa without carbidopa and entacapone, absorption is greater and elimination is slower than in young subjects. However, when combined with carbidopa, the absorption of levodopa is similar in both elderly and the young patients, although the AUC is still 1.5 times greater in the elderly due to decreased DDC activity and lower clearance caused by aging. There are no significant differences in the AUC of carbidopa or entacapone between younger (45–64 years) and elderly subjects (65–75 years).

Gender

The 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 the elimination phases (see section CONTRAINDICATIONS). No specific studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment have been reported.

Renal impairment

Renal impairment does not affect the pharmacokinetics of entacapone. No specific 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 POSOLOGY AND METHOD OF ADMINISTRATION).

PRECLINICAL SAFETY DATA

Preclinical data for 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 probably 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.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

Tablet core: croscarmellose sodium, magnesium stearate, maize starch, mannitol, povidone

Film-coating: glycerol 85%, hypromellose, magnesium stearate, polysorbate 80, red iron oxide (E 172), sucrose, titanium dioxide (E 171), yellow iron oxide (E 172). (Note: yellow iron oxide not used in 200 mg/50 mg/200 mg tablets).

Pharmaceutical formulations may vary between countries.

INCOMPATIBILITIES

Not applicable.

SPECIAL PRECAUTIONS FOR STORAGE

See folding box.

Stalevo should not be used after the date marked “EXP” on the pack.

INSTRUCTIONS TO USE AND HANDLING

Note: Stalevo must be kept out of the reach and sight of children.

NATURE AND CONTENT OF CONTAINER

Stalevo 50 mg/12.5 mg/200 mg: HDPE bottle of 10, 30, 100 or 250 tablets.

Stalevo 100 mg/25 mg/200 mg: HDPE bottle of 10, 30, 100 or 250 tablets.

Stalevo 150 mg/37.5 mg/200 mg: HDPE bottle of 10, 30, 100 or 250 tablets.

Stalevo 200 mg/50 mg/200 mg: HDPE bottle of 10, 30, or 100 tablets.

Certain pack size may not be available in all countries

Manufacturer:

See folding box.

Package Leaflet

Information issued: May 2019.SIN

Novartis Pharma AG, Basel, Switzerland