STALEVO PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORM

STALEVO® 50/12,5 Film-coated tablets

STALEVO® 100/25 Film-coated tablets

STALEVO® 150/37,5 Film-coated tablets

COMPOSITION

The available dose strengths of levodopa and carbidopa in 4:1 ratio are 50/12,5 mg, 100/25 mg and 150/37,5 mg combined with 200 mg of entacapone in each tablet.

STALEVO 50/12,5 Film-coated tablets:

Each film-coated tablet contains 50 mg levodopa, 12,5 mg carbidopa and 200 mg entacapone.

STALEVO 100/25 Film-coated tablets:

Each film-coated tablet contains 100 mg levodopa, 25 mg carbidopa and 200 mg entacapone.

STALEVO 150/37,5 Film-coated tablets:

Each film-coated tablet contains 150 mg levodopa, 37,5 mg carbidopa and 200 mg entacapone.

Excipients:

Tablet core: croscarmellose sodium, magnesium stearate, maize starch, mannitol, povidone K 30.

Film-coating: glycerol 85 %, hypromellose, magnesium stearate, polysorbate 80, red iron oxide (E172), sucrose, titanium dioxide (E171), yellow iron oxide (E172).

PHARMACOLOGICAL CLASSIFICATION

A 5.4.1 Anti-parkinsonism preparations.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Each tablet contains a combination of the three active ingredients: levodopa, carbidopa and entacapone. Carbidopa is a peripheral dopa decarboxylase (DDC) inhibitor, and entacapone is a peripheral catechol-O-methyltransferase (COMT) inhibitor. Both reduce the extensive peripheral metabolism of levodopa, thereby improving its availability to the brain.

Levodopa, the precursor of dopamine, belongs to dopaminergic agents therapeutic group. Carbidopa, a dopa decarboxylase (DDC) inhibitor, and entacapone, a catechol-O-methyl transferase (COMT) inhibitor, both modify the therapeutic properties of levodopa but have no therapeutic activity without levodopa.

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 increased 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 effects such as nausea is reduced.

With 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). 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 reversibility of COMT inhibition with entacapone has been demonstrated in bioassays of COMT activity in red blood cells; red blood cell COMT inhibition tightly correlates with plasma concentrations of the medicine.

Pharmacokinetic properties:

a) 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 ingredients, the bioavailability for levodopa is 15 to 33 %, for carbidopa 40 to 70 % and for entacapone 29 to 36 % (35 % after the 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 (0,36 to 1,6 litres/kg) and entacapone (0,27 litres/kg) is moderately small while no data for carbidopa are available.

With STALEVO in healthy male and female volunteers aged 45 to 75 years, the C_{max} for entacapone was reached at about one hour and the C_{max} for carbidopa at about 2 to 3 hours after oral dosing. Levodopa's pharmacokinetic characteristics are summarised in *Table 2.*

Table 2: Pharmacokinetic characteristics of levodopa on different tablet strengths of STALEVO in healthy elderly subjects (mean ± SD)

Tablet strength*	**AUC0-∞ (ng·h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**

12,5 – 50 – 200 mg 25 – 100 – 200 mg 37,5 – 150 – 200 mg	1044 ± 314 2906 ± 715 3773 ± 1118	437 ± 154 975 ± 247 1272 ± 329	1,1 ± 0,5 1,4 ± 0,6 1,5 ± 0,9

* Carbidopa/ levodopa/ entacapone

Levodopa is bound to plasma protein only to a minor extent (about 10 to 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 medicines (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these medicines 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 (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid) 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; only about 0,2 % is excreted unchanged in urine. The main metabolic pathway is glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5 % of plasma total amount. 10 % of an entacapone dose is excreted in urine, and 90 % in faeces by biliary excretion. Of entacapone metabolites found in urine only about 1 % has been formed through oxidation.

Total clearance for levodopa is in the range of 0,55 to 1,38 litres/kg/h and for entacapone is in the range of 0,70 litres/kg/h. The elimination-half life (t1/2el) is 0,6 to 1,3 hours for levodopa, 2 to 3 hours for carbidopa and 0,4 to 0,7 h for entacapone, each given separately

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

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*).

b) 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 subjects. However, after combination of carbidopa with levodopa, the absorption of levodopa is similar between the elderly and the young, but the AUC is still 1,5 fold greater in the elderly due to decreased DDC inhibitor activity and lower clearance by aging. Entacapone pharmacokinetics is independent of age.

In the pharmacokinetic studies with STALEVO there was no significant difference in the AUC of levodopa, carbidopa, or entacapone between younger (45 to 60 years) and elderly subjects (60 to 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 *Dosage and Directions for use and Contraindications*). No specific studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment have been reported, however, it is advised that STALEVO should be administered cautiously to patients with mild to moderate hepatic impairment.

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 *Contraindications*).

INDICATIONS

STALEVO is indicated for the treatment of patients with Parkinson's disease who have end-of-dose motor fluctuations.

CONTRAINDICATIONS

- Known hypersensitivity to levodopa, carbidopa or entacapone or any of the excipients of the STALEVO (see *Composition*).
- Pregnancy and breastfeeding (see *Pregnancy and lactation*).
- Severe hepatic impairment.
- Narrow-angle glaucoma.
- Suspicious undiagnosed skin lesions or history of melanoma.
- Pheochromocytoma due to the increased risk of hypertensive crisis.

- Co-administration of STALEVO with a non-selective monoamine oxidase (MAO-A and MAO-B) inhibitor e.g. (phenelzine, tranylcypromine, linezolid).
- Co-administration of a selective MAO-A inhibitor and a selective MAO-B inhibitor (see section *Interactions*). These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with STALEVO.
- A history of Neuroleptic Malignant Syndrome (NMS) and/or non – traumatic rhabdomyolysis.

WARNINGS AND SPECIAL PRECAUTIONS

STALEVO is not recommended for the treatment of medicine-induced extrapyramidal reactions.

Due to levodopa, STALEVO therapy should be administered cautiously to patients with ischaemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.
The incidence rates of myocardial infarction and other ischaemic 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.

Care should be exercised when administering levodopa treatment to patients with a history of myocardial infarction that has residual atrial nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustments.
All patients treated with STALEVO should be monitored carefully for the development of mental changes (e.g. hallucinosis and psychoses), depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current psychosis should be treated with caution.

Concomitant administration of antipsychotic medicines with dopamine receptor-blocking properties particularly D2 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 *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 medications may need to be adjusted when STALEVO treatment is introduced in 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. 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 creatinine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. 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 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.

Because of the mechanism of action of entacapone, STALEVO may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action.

Thus, STALEVO should be administered cautiously to patients being treated with medicinal products metabolised by COMT or products releasing catecholamines, e.g. rimiterole, isoprenaline, ephedrine, adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, dobutamine, alpha-methyldopa, and apomorphine (see also section *Interactions*).

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 diarrhoea, monitoring weight is recommended in order to avoid excessive weight decrease. Prolonged or persistent diarrhoea suspected to be related to STALEVO may be a sign of colitis. In the event of prolonged or persistent diarrhoea, the medicine 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. Pathological gambling, increased libido and hypersexuality have been reported in Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments including STALEVO.

Levodopa/carbidopa may cause false positive result when a dipstick is used to test for urinary ketone; 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 STALEVO.

There is some evidence suggesting that the risk to develop prostate cancer may be increased in patients treated with STALEVO.

Effects on the ability to drive and use machines

STALEVO (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.

INTERACTIONS

To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian medicines with STALEVO therapy. Caution should be exercised when the following medicines are administered concomitantly with levodopa therapy.

Other antiparkinsonian medicines:

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 other entacapone containing products.

Antihypertensive medicines:

Symptomatic postural hypotension may occur when levodopa, as in STALEVO, is added to the treatment of patients already receiving antihypertensive medicines. 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. (See *Contraindications* for patients

receiving MAO inhibitors). 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 medicines including, 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 *Contraindications* and *Special precautions for use*).

Other medicines:

Dopamine receptor antagonists (e.g. some antipsychotics and antiemetics), phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these medicines with STALEVO should be carefully observed for loss of therapeutic response.

Due to entacapone's affinity to cytochrome P450 2C9 *in vitro* (see *Pharmacokinetic properties*), STALEVO may potentially interfere with medicines 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 to 26 %]. The INR values increased on average by 13 % [CI_{90} 6 to 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 to 3 hours apart (see *Side-effects*).

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

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 LACTATION

STALEVO is contraindicated in pregnancy and lactation.

Pregnancy:

There are no adequate data from the use of the combination of levodopa/ carbidopa/entacapone in pregnant patients. Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. The potential risk for humans is unknown. STALEVO should not be used during pregnancy (see *Contraindications*).

Lactation:

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 unknown. Women should not breastfeed during treatment with STALEVO (see *Contraindications*).

DOSAGE AND DIRECTIONS FOR USE

Method of administration:

Each STALEVO tablet is to be taken orally as one dose either with or without food (see *Pharmacokinetic properties*). One tablet contains one treatment dose. The tablets should always be swallowed whole.

The optimum daily dosage of STALEVO must be determined by careful titration of levodopa in each patient. The daily dose of STALEVO should preferably be optimised using one of the tablet strengths available of STALEVO (50/12,5/200 mg, 100/25/200 mg, or 150/37,5/200 mg levodopa/carbidopa/ entacapone).

Patients should be instructed to take only one STALEVO tablet per dose administration. Patients receiving less than 70 to 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, therefore the maximum STALEVO dose is 10 tablets per day.

As with levodopa/ carbidopa, nonselective 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 recommended dose in the package insert of MAO inhibitors with selectivity for MAO type B (e.g. selegiline HCl).

How to switch 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 switched to corresponding STALEVO tablets.

For example, a patient taking one tablet of 100/25 mg of levodopa/carbidopa with one tablet of entacapone 200 mg four times daily can take one 100/25/200 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 100/25/200 mg, (or 50/12,5/200 mg, or 150/37,5/200 mg) tablets, 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. Begin with a dosage of STALEVO that will provide either the same amount of levodopa or slightly (5 to 10 %) more.

d) As there is limited experience in transferring patients currently treated with controlled release formulations of levodopa/DDC inhibitor to STALEVO, careful titration for optimal clinical response is recommended.

How to switch patients not currently treated with entacapone to STALEVO:

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 800 mg per day. 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 to 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 described in *Dosage and directions for use*.

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 (see *Dosage and directions for use*).

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.

Children and adolescents:

The safety and efficacy of STALEVO in patients under 18 years of age has not been established.

Elderly:

No dosage adjustment of STALEVO is required for elderly patients. The posological recommendations above reflect the wide experience and clinical data derived from the use of levodopa/carbidopa combined with entacapone in elderly patients.

Hepatic impairment:

Caution is recommended when administering STALEVO to patients with mild to moderate hepatic

impairment. Dose reduction may be necessary (See *Pharmacological action* and *Contraindications).*

Renal insufficiency:

Renal insufficiency does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency. STALEVO therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapy.

SIDE-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 clinical trials consisting of 1810 patients treated with Stalevo or entacapone combined 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
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
Eye disorders	
Common:	Blurred vision
Cardiac disorders	
Common:	Ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris)**, dysrhythmias
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
Skin and subcutaneous tissue disorders	
Common:	Rash, hyperhidrosis
Uncommon:	Discolourations other than urine (e.g. skin, nail, hair, sweat)
Rare:	Angioedema
Musculoskeletal and connective tissue disorders	
Very common:	Muscle, musculoskeletal and connective tissue pain
Common:	Muscle spasms, arthralgia
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
**The incidence rates of myocardial infarction and other ischaemic 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.	

Post-marketing

The following adverse reactions, listed in Table 2, have been accumulated from the post-marketing data since the introduction of entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor].

Table 2: Adverse reactions	
Psychiatric disorders	
Not known:	Suicidal behaviour
Nervous system disorders	
Not known:	Neuroleptic malignant syndrome
Hepatobiliary disorders	
Not known:	Hepatitis with mainly cholestatic features
Skin and subcutaneous tissue disorders	
Not known:	Urticaria
Musculoskeletal and connective tissue disorders	
Not known:	Rhabdomyolysis

c. Description of selected adverse reactions

Some of the adverse reactions in Table 1 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. Adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may cause also discolouration of e.g. skin, nail, hair and sweat.

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

Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as STALEVO, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido, hypersexuality and other urges, generally reversible upon reduction of the

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Cases of overdose of 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, discolouration of skin, tongue and conjunctiva, and chromaturia.

Management of acute overdosage with STALEVO therapy 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 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 dysrhythmias. If required, appropriate, anti-dysrhythmic therapy should be given. The possibility that the patient has taken other medicines in addition to STALEVO should be taken into consideration. The value of dialysis in the treatment of overdosage is not known.

IDENTIFICATION

STALEVO® 50/12,5 Film-coated tablets:

Film-coated tablet, brownish- or greyish-red, round, biconvex tablets marked with “LCE 50” on one side. Diameter 11 mm.

STALEVO® 100/25 Film-coated tablets:

Film-coated tablet, brownish- or greyish-red, oval, tablets marked with “LCE 100” on one side. Diameter 7,6 x 16,3 mm.

STALEVO® 150/37,5 Film-coated tablets:

Film-coated tablet, brownish- or greyish-red, elongated-ellipse shaped tablets marked with “LCE 150” on one side. Diameter 9,3 x 14,31 mm.

PRESENTATION

Pack sizes:

100 tablets packed into white HDPE plastic containers with tamper evident PP plastic closures.

Heat sealable aluminium foil innerseals.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep the container well-closed and store in a dry place protected from light.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

STALEVO® 50/12,5 Film-coated tablets: 38/5.4.1/0067

STALEVO® 100/25 Film-coated tablets: 38/5.4.1/0138

STALEVO® 150/37,5 Film-coated tablets:38/5.4.1/0137

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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