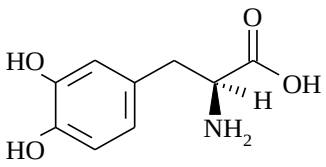
STALEVO®

levodopa/carbidopa anhydrous/entacapone

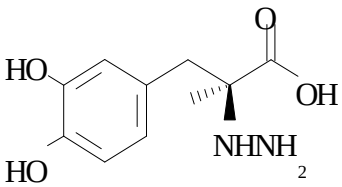
NAMES OF THE MEDICINES

AAN: Levodopa
Structural formula:



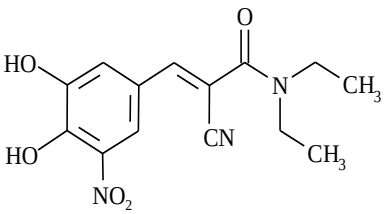
Chemical name: (2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid
Molecular formula: $C_9H_{11}NO_4$
Molecular weight: 197.19
CAS number: 59-92-7

AAN: Carbidopa anhydrous
Structural formula:



Chemical name: (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid, monohydrate
Molecular formula: $C_{10}H_{14}N_2O_4$
Molecular weight: 226.2
CAS number: 31823-41-3

AAN: Entacapone
Structural Formula:



Chemical name:	(E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide
Molecular formula:	$C_{14}H_{15}N_3O_5$
Molecular weight:	305.28
CAS number:	130929-57-6

DESCRIPTION

Levodopa and carbidopa are white crystalline compounds, slightly soluble in water. Entacapone is a yellow or greenish yellow crystalline powder. The (*E*)-isomer is the main product and less than 0.5% of the (*Z*)-isomer occurs in the raw material.

Stalevo film-coated tablets are available in six strengths, each containing a 4:1 ratio of levodopa to carbidopa anhydrous combined with 200 mg of entacapone in a standard release formulation: 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg and 200/50/200 mg.

Each strength of Stalevo tablets contains the following excipients: croscarmellose sodium, magnesium stearate, starch - maize, mannitol, povidone, glycerol, hypromellose, polysorbate 80, iron oxide red CI77491, sucrose, titanium dioxide, iron oxide yellow CI77492. Iron oxide yellow CI77492 is not present in the 75/18.75/200 mg, 125/31.25/200 mg, 200/50/200 mg tablets.

PHARMACOLOGY

Pharmacodynamics

The symptoms of Parkinson's disease are thought to be 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 dopa decarboxylase (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 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), 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 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 drug.

Pharmacokinetics

Absorption and 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 - 33 %, for carbidopa 40 -70 % and for entacapone 29 - 36 % (35 % after the 200 mg oral dose). High protein 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 effect of food on Stalevo tablets has not been evaluated.

Levodopa: The pharmacokinetic characteristics of levodopa following the administration of single-dose Stalevo tablets are summarised in Table 1.

Table 1. **Pharmacokinetic characteristics of levodopa with different tablet strengths of Stalevo in healthy elderly subjects (mean ±SD)**

Tablet strength*	**$AUC_{0-\infty}$ (ng·h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
50/12.5/200 mg	1044 ± 314	473 ± 154	1.1 ± 0.5
100 /25/200 mg	2906 ± 715	975 ± 247	1.4 ± 0.6
150/37.5/200 mg	3774 ± 1118	1272 ± 329	1.5 ± 0.9

* levodopa/carbidopa anhydrous/entacapone

Levodopa is bound to plasma protein only to a minor extent of about 10-30 %.

Carbidopa: Following administration of Stalevo as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5 to 3.4 hours on average. The mean C_{max} ranged from about 40 to 125 ng/mL and the mean AUC from 170 to 700 ng.h/mL, with different Stalevo strengths providing 12.5 mg, 25 mg or 37.5 mg of carbidopa anhydrous. Carbidopa is bound approximately 36 % bound to plasma protein.

Entacapone: Following administration of Stalevo as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0 to 1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/mL and the AUC 1250 to 1450 ng.h/mL after administration of different Stalevo strengths all providing 200 mg entacapone. Entacapone is extensively bound to plasma proteins (about 98 %), mainly to serum albumin. The distribution volumes of both levodopa (0.36 - 1.6 L/kg) and entacapone (0.27 L/kg) are moderately small while no data for carbidopa are available.

Metabolism and elimination:

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC_{50} ~ 4 µM). Entacapone showed little or no

inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (see "PRECAUTIONS - Interactions with Other Drugs").

Levodopa: The elimination-half life ($t_{1/2el}$) is 0.6 - 1.3 hours for levodopa. 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: The elimination-half life ($t_{1/2el}$) is 2 -3 hours for carbidopa. 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: The elimination-half life is ($t_{1/2el}$) 0.4 - 0.7 hours for entacapone. 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. Ten percent of an entacapone dose is excreted in urine, and 90 % in faeces by biliary excretion. Of entacapone metabolites found in urine only about 1 % have been formed through oxidation. Total plasma 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.

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

Pharmacokinetics in patients with liver impairment:
Stalevo should be administered cautiously to patients with biliary obstruction or hepatic disease. There are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment, but biliary excretion appears to be the major route of excretion of entacapone.

Entacapone: Hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200mg entacapone was administered alone. A single 200mg dose of entacapone, without levodopa/DDI inhibitor co-administration, showed approximately twofold higher AUC and C_{max} values in patients with a history of alcoholism and hepatic impairment (n=10) compared to normal subjects (n=10). All patients had biopsy-proven liver cirrhosis caused by alcohol. According to Child-Pugh grading 7 patients with liver disease had mild hepatic impairment and 3 patients had moderate hepatic impairment. As only about 10% of the entacapone dose is excreted in urine, as parent compound and conjugated glucuronide, biliary excretion appears to be the major route of excretion of this drug. Consequently, Stalevo should be administered with care to patients with biliary obstruction or hepatic disease.

Pharmacokinetics in patients with renal impairment:
Stalevo should be administered cautiously to patients with severe renal disease (see "DOSAGE AND ADMINISTRATION"). There are no studies 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.

Entacapone: No important effects of renal function on the pharmacokinetics of entacapone were found. The pharmacokinetics of entacapone have been investigated after a single 200-mg entacapone dose, without levodopa-dopa decarboxylase inhibitor co-administration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12 mL/sec/1.73 m^2), moderate impairment (n=10; creatinine clearance ranging from 0.60 - 0.89 mL/sec/1.73 m^2), and severe impairment (n=7; creatinine clearance ranging from 0.20 - 0.44 mL/sec/1.73 m^2).

Pharmacokinetics in the elderly:
Stalevo tablets have not been studied in Parkinson's disease patients or in healthy volunteers older than 75 years old. In the pharmacokinetics studies conducted in healthy volunteers following single dose of carbidopa/levodopa/entacapone (as Stalevo or as separate carbidopa/levodopa and Comtan tablets):

Levodopa: The AUC of levodopa is significantly (on average 10 - 20%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of levodopa between younger (45–60 years) and elderly subjects (60–75 years).

Carbidopa: There is no significant difference in the C_{max} and AUC of carbidopa, between younger (45 – 60 years) and elderly subjects (60–75 years).

Entacapone: The AUC of entacapone is significantly (on average, 15%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of entacapone between younger (45–60 years) and elderly subjects (60–75 years).

Gender differences in pharmacokinetics:
The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and/or entacapone. 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. Following a single dose of carbidopa, levodopa and entacapone together, either as STALEVO or as separate carbidopa/ levodopa and Comtan tablets in healthy volunteers (age range 45-74 years).

Levodopa: The plasma exposure (AUC & C_{max}) of levodopa is significantly higher in females than males (on average, 40% for AUC and 30% for C_{max}). These differences are primarily explained by body weight. Other published literature showed significant gender effect (higher concentrations in females) even after correction for body weight.

Carbidopa: There is no gender difference in the pharmacokinetics of carbidopa.

Entacapone: There is no gender difference in the pharmacokinetics of entacapone.

CLINICAL TRIALS

Each Stalevo tablet, provided in six single-dose strengths, contains carbidopa anhydrous and levodopa in a 1:4 ratio and a 200 mg dose of entacapone. Four Stalevo strengths 50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg and 200/50/ 200 mg have been shown to be bioequivalent to the corresponding doses of standard-release levodopa/carbidopa anhydrous 100/25 mg tablets and entacapone 200 mg tablets. Hence, the results from previous trials of entacapone 200 mg administered concomitantly with standard levodopa/carbidopa preparations are applicable to the effects of Stalevo, as well.

The anticipated therapeutic effects of Stalevo are based on the results of two pivotal Phase III studies in 376 Parkinson's disease patients with end-of-dose motor fluctuations receiving entacapone or placebo with each levodopa/DDC inhibitor dose.

The two pivotal Phase III studies, entitled NOMECOMT and SEESAW, were prospective, randomised, double blind, placebo controlled, parallel group trials, each conducted over a 6-month period. In the two studies, a total of 188 patients in the entacapone group and 188 patients in the placebo group were included in the "intention to treat" analysis. The mean duration of Parkinson's disease in subjects prior to trial entry was 10-11 years and the duration of fluctuations in motor performance was >4 years. A tablet of entacapone 200 mg or placebo was administered in combination with each patient's usual scheduled dose of levodopa/DDC inhibitor (4 to 10 doses daily). The primary efficacy parameter was the increase in mean daily "ON" time or proportion of "ON" time (from the home diaries) compared to placebo. In the NOMECOMT study, the duration of "ON" time following the first daily dose of levodopa was also a primary parameter. Of secondary importance were evaluations of "OFF" time, the UPDRS, global score, daily fluctuations and daily levodopa dosage.

In both studies, entacapone had a significant positive effect on the primary, and most of the secondary efficacy parameters. In the NOMECOMT study, the mean daily "ON" time was 1.3 hours (approximately 14%) longer in the entacapone group relative to placebo ($p<0.001$). The percent of "ON" time while awake increased significantly ($p<0.001$) and the duration of "ON" time after the first daily dose was also significantly longer ($p<0.05$). In the SEESAW study, although the increase in daily "ON" time of 0.6 hours did not reach statistical significance, the "ON" time expressed as a percent of time awake was significantly improved ($p<0.05$). The UPDRS objective disease rating (total, activities of daily living, motor parts) and the global evaluation by the investigator were significantly in favour of entacapone in both studies, and the daily dose of levodopa required decreased by approximately 100 mg per day ($p<0.001$). At the end of the active treatment period, a well defined withdrawal effect of entacapone was demonstrated, with the outcome for all variables showing a significant deterioration in the patients' condition. The average daily "ON" time decreased by 1.5 hours ($p<0.001$) and the motor score of the UPDRS deteriorated significantly ($p<0.01$) in both studies.

INDICATIONS

Stalevo is indicated for the management of patients with Parkinson's disease who are experiencing motor fluctuations.

CONTRAINDICATIONS

- Known hypersensitivity to the active substances or to any of the excipients.
- Pregnancy and breast feeding (see "PRECAUTIONS - Use in Pregnancy and Use in Lactation")
- Severe liver impairment (see "PHARMACOLOGY – Pharmacokinetics in patients with liver impairment")
- Patients with narrow-angle glaucoma
- Patients with phaeochromocytoma due to the increased risk of hypertensive crisis.
- Co-administration of Stalevo with non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine) is contraindicated. Similarly, co-administration of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and Stalevo is contraindicated.
- A previous history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis (see "PRECAUTIONS - Neuroleptic Malignant Syndrome and Rhabdomyolysis").
- Because levodopa may activate malignant melanoma, Stalevo should not be used in patients with suspicious undiagnosed skin lesions or a history of malignant melanoma.

PRECAUTIONS

Precautions Relating to Levodopa Component of Stalevo

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

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

All patients treated with levodopa 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 antipsychotic drugs with dopamine receptor-blocking properties particular D_2 receptor antagonists should be carried out with caution and the patient

carefully observed for loss of antiparkinsonian effect or worsening of antiparkinsonian 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 "Effects on ability to drive and use machines").

Neuroleptic Malignant Syndrome and Rhabdomyolysis

Neuroleptic Malignant Syndrome (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 the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatinine 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 (see 'DOSAGE AND ADMINISTRATION – Discontinuation of Stalevo therapy'). Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment. 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.

Diarrhoea Anorexia, Asthenia and Weight Loss

For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential 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 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.

Impulse Control Disorders

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, medication use and punding (repetitive purposeless activity) 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.

Hallucinations

Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials of entacapone, hallucinations developed in approximately 4.0% of patients treated with 200 mg entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg entacapone and placebo, respectively. Hallucinations led to hospitalisation in 1.0% and 0.3% of patients in the 200 mg entacapone and placebo groups, respectively.

Dyskinesia

Entacapone may potentiate the dopaminergic side effects of levodopa and may therefore cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates were 1.5% and 0.8% for 200 entacapone and placebo, respectively.

Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other non-ergot derived drugs (eg. entacapone, levodopa) that increase dopaminergic activity can cause them is unknown. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; three of these patients were also treated with pergolide and one with bromocriptine. The duration of treatment with entacapone ranged from 7-17 months.

General Anaesthesia

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.

Patient Monitoring

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

Concurrent Diseases

Stalevo should be administered cautiously to patients with biliary obstruction, hepatic disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease.

Use in Combination with Other Antiparkinsonian Medications

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 patients who received placebo in combination with any of these medications. The doses of other antiparkinsonian medications may require adjustment when Stalevo is being substituted in patients not currently taking entacapone.

Effects on Ability to Drive or Operate Machinery

Stalevo may cause dizziness, somnolence and episodes of sudden sleep onset, and symptomatic orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. The ability of patients with Parkinson's disease to drive or operate machinery should be evaluated by the treating physician.

Stalevo may have a major influence on the ability to drive and use machines. Patients being treated with Stalevo 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 "PRECAUTIONS").

Use in Children and Adolescents (age < 18 years)

Stalevo is not recommended for use in children below age 18 due to lack of data on safety and efficacy.

Use in Pregnancy (Pregnancy Category B3)

There are no adequate data from the use of combination levodopa/carbidopa/entacapone in pregnant women. In rats and rabbits, co-administration of levodopa, carbidopa and entacapone during the period of organogenesis at oral doses of less than (levodopa, carbidopa) and twice (entacapone) the intakes on a mg/m^2 basis at the recommended human dose of Stalevo, was not teratogenic. Levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. No teratogenicity was observed following administration of entacapone to pregnant rats and rabbits during the period of

organogenesis at oral doses producing respective maternal exposures (plasma AUC) of 40 times, and marginally greater than, the maximal clinical exposure. In pregnant rabbits, fetotoxicity and abortions occurred at maternal exposures less than the maximal clinical exposure. The extent of placental transfer of entacapone and its metabolites in animals and humans is unknown, and there is no experience of the use of entacapone in pregnant women. Hence, the use of Stalevo during pregnancy is contraindicated.

Use in Lactation

In animal studies, carbidopa and entacapone were excreted in milk. Oral administration of entacapone to rats from early pregnancy to weaning reduced offspring bodyweight at maternal exposure (plasma AUC) of 26 times the maximal clinical exposure, but not at an exposure of six times the maximal clinical exposure. It is not known whether levodopa, carbidopa, or entacapone is excreted in human milk. Therefore, Stalevo is contraindicated for nursing mothers.

Carcinogenicity

Two year carcinogenicity studies were conducted in mice and rats dosed orally with entacapone daily. No carcinogenic effects were found in the rodents at exposures (plasma AUC) of at least 6 times the maximal clinical exposure, except for an increased incidence of renal tubule tumours in male rats at the highest dose. The tumours were induced by a disturbance in the renal hydrolysis of a protein (α2μ-globulin) specific to male rats, and are thought not to constitute a hazard for clinical use.

Genotoxicity

Entacapone was not genotoxic in a bacterial gene mutation assay, but positive results were obtained in a mammalian gene mutation assay and an in vitro assay for clastogenicity. Entacapone was negative in an *in vivo* assay for clastogenicity and assays for DNA damage. Carbidopa was positive in bacterial and mammalian gene mutation assays, but negative in an *in vivo* assay for clastogenicity. A combination of levodopa, carbidopa and entacapone was negative in a bacterial gene mutation assay and two *in vivo* assays for clastogenicity.

Impairment of Fertility

Oral administration of entacapone to male and female rats prior to and during mating did not affect reproductive parameters at exposures (plasma AUC) up to 26 times the maximal clinical exposure.

INTERACTIONS WITH OTHER MEDICINES

Caution should be exercised when the following drugs are administered concomitantly with Stalevo therapy.

Antihypertensive Drugs

Symptomatic postural hypotension may occur when levodopa is added to the treatment of patients already receiving antihypertensive drugs. 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 "DOSAGE AND ADMINISTRATION"). No interactions were observed between entacapone and imipramine and between entacapone and moclobemide in single dose studies in healthy volunteers.

MAO Inhibitors
For patients receiving nonselective MAO inhibitors see "CONTRAINDICATIONS".

Selegiline
No interactions were observed between entacapone and selegiline in repeated-dose studies in patients with Parkinson's disease. Entacapone may be used in combination with selegiline (a selective MAO-B inhibitor), but the daily dose should not exceed 10 mg.

Warfarin
Due to entacapone's affinity to cytochrome P450 2C9 *in vitro* (see "Pharmacokinetics – Metabolism and Elimination"), Stalevo may potentially interfere with drugs 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 International Normalised Ratio (INR) values increased on average by 13 % [CI_{90} 6-19 %]. Thus, control of INR is recommended when Stalevo is initiated for patients receiving warfarin.

Dopamine D2 Receptor Antagonists
Dopamine D2 receptor antagonists (eg. phenothiazines, butyrophenones, risperidone and isoniazid) may reduce the therapeutic effects of levodopa.

Phenytoin and Papaverine
Phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these drugs with Stalevo should be carefully observed for loss of therapeutic response.

Metoclopramide
Although metoclopramide may increase the bioavailability of levodopa by increasing the gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Pyroxidine
Stalevo can be given to patients receiving supplemental pyroxidine. Oral coadministration of 10-25 mg of pyroxidine hydrochloride (vitamin B6) with levodopa may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyroxidine; therefore, Stalevo can be given to patients receiving supplemental pyroxidine.

Drugs Metabolised by COMT

Because of its mechanism of action, entacapone may interfere with the metabolism of drugs containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with drugs metabolised by COMT (e.g. isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine, paroxetine). Patients should be carefully monitored if entacapone is administered in combination with any of these drugs.

When a single 400 mg dose of entacapone was given together with intravenous isoprenaline and adrenaline without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and adrenaline respectively. Therefore, drugs known to be metabolised by COMT, such as isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, methyldopa and apomorphine should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Food

Levodopa competes with certain amino acids, and so its absorption from Stalevo may be impaired in some patients on a high protein diet.

Other Forms of Interactions

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 "ADVERSE EFFECTS").

In pharmacokinetic studies at therapeutic concentrations, entacapone does not displace other extensively bound drugs (e.g. warfarin, salicylic acid, phenylbutazone and diazepam), nor is it displaced to any significant extent by any of these drugs at therapeutic or higher concentrations. However, entacapone binds to human albumin binding site II, which also binds several other medicinal products, including diazepam and ibuprofen. Clinical interaction studies with diazepam and non-steroidal anti-inflammatory drugs have not been carried out.

As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine and some antibiotics (eg. erythromycin, rifampicin, ampicillin and chloramphenicol).

Sucrose

Stalevo tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Stalevo tablets.

ADVERSE EFFECTS

Stalevo combines levodopa/carbidopa and entacapone in one product. The following section describes the undesirable effects reported for levodopa/carbidopa and for entacapone used in combination with levodopa/DDC inhibitor.

Levodopa / Carbidopa

Adverse effects that occur frequently with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction.

More common reactions: The most common adverse effects are dyskinesias including choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs to consider levodopa dosage reduction. Nausea is also related to enhanced central dopaminergic activity, is a common adverse effect of levodopa/carbidopa.

Other adverse effects associated with levodopa/carbidopa therapy are mental changes, including paranoid ideation and psychotic episodes; depression, with or without development of suicidal tendencies; and cognitive dysfunction. Adding entacapone to levodopa/DDC inhibitor therapy (carbidopa or benserazide), e.g. initiation of Stalevo treatment in an entacapone naive patient may affect the occurrence of some of these mental changes (see Table 2 - Psychiatric disorders).

Less common reactions: Less frequent adverse effects of levodopa/carbidopa therapy are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence.

Gastrointestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, chest pain, dyspnoea and paraesthesia have occurred rarely with levodopa/carbidopa.

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 ‘PRECAUTIONS – Impulse Control Disorders’).

Other adverse effects that have been reported with levodopa and may, therefore, be potential adverse effects of Stalevo as well, include:

Neurological: Ataxia, numbness, increased hand tremor, muscle twitching, muscle cramp, trismus, activation of latent Horner's syndrome, falling, gait abnormalities.

Psychiatric events: Confusion, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.

Gastrointestinal: Dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain, constipation, diarrhoea, flatulence, burning sensation of the tongue.

Metabolic: Weight gain or loss, oedema.

Skin and subcutaneous tissue: Flushing, increased sweating, dark sweat, rash, hair loss.

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Eye: Diplopia, blurred vision, dilated pupils, oculogyric crises.

Miscellaneous: Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome (see "CONTRAINDICATIONS"), malignant melanoma.

Entacapone

The most frequent adverse reactions caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of the treatment. Reduction of levodopa dosage usually decreases the severity and frequency of the reactions. The other major class of adverse reactions are gastrointestinal symptoms, including nausea, vomiting, abdominal pain, constipation and diarrhoea. Urine may be discoloured reddish-brown by entacapone but this is a harmless phenomenon.

Usually the adverse reactions caused by entacapone in combination with levodopa/DDC inhibitor are mild to moderate. In clinical studies the most common adverse reactions leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea) and increased dopaminergic adverse reactions of levodopa (e.g. dyskinesias). Entacapone in association with levodopa has been associated with isolated episodes of excessive daytime somnolence and sudden sleep onset.

Isolated cases of neuroleptic malignant syndrome (NMS) have been reported especially following abrupt reduction or discontinuation of entacapone and other dopaminergic medications.

Isolated cases of rhabdomyolysis have been reported.

Dyskinesias, nausea, diarrhoea, abdominal pain and dry mouth were reported significantly more often with entacapone than with placebo (Table 2), based on pooled data from clinical studies involving 603 patients taking levodopa/DDC inhibitor and entacapone and 400 patients taking levodopa/DDC inhibitor therapy and placebo. Other common adverse events (incidence < 3%) included sleep disturbances and paroniria. Serious adverse events

(incidence > 0.3% and ≥ placebo) that do not appear in Table 2 included chest pain, pneumonia, confusion and dyspnoea.

Table 2. Adverse reactions reported with a frequency of ≥ 3% in double-blind placebo controlled phase III studies of entacapone.

Body system	Entacapone % (n = 603)	Placebo % (n = 400)
Autonomic nervous system:		
Hypotension - postural	2.7	3.0
Body as a whole:		
Fatigue	6.1	3.5
Pain	6.0	4.5
Back pain	5.0	3.0
Headache	3.5	4.3
Falls	4.1	3.5
Sweating increased	3.6	3.0
Gastrointestinal system:		
Nausea	13.8	7.5
Diarrhoea	10.0	4.0
Abdominal pain	8.1	4.5
Constipation	6.3	4.3
Vomiting	4.0	1.0
Dry mouth	3.0	0.3
Nervous system:		
Dyskinesia	25.2	14.8
Parkinsonism aggravated	13.9	14.8
Hyperkinesia	9.5	5.0
Hypokinesia	8.6	7.5
Dizziness	7.5	6.0
Tremor	5.0	6.5
Dystonia	3.0	4.3
Leg cramps	3.0	3.5
Vertigo	2.3	3.3
Psychiatric disorders:		
Insomnia	6.3	7.3
Hallucinations	4.1	4.0
Depression	3.2	3.3
Urinary system:		
Urine colour abnormal	9.5	0.0

Some of the adverse reactions, such as dyskinesia, nausea, and abdominal pain, may be more common with higher doses of entacapone (1,400 to 2,000 mg per day) than with lower doses of entacapone.

Incidence Rates of Myocardial Infarction and other Ischemic Heart Disease Events in a Meta-analysis

Myocardial infarction and other ischemic heart disease events have been reported with the use of entacapone in combination with carbidopa/levodopa. A meta-analysis of 13 controlled, double-blind studies in patients with end-of-dose motor fluctuations ("wearing-off") was conducted. In 2082 patients treated with entacapone, the results of the meta-analysis showed incidence rates of 0.43% (95% CI 0.20% - 0.82%) and 1.54% (95% CI 1.05% - 2.16%) for myocardial infarction and other ischemic heart disease events, respectively. Based on the risk difference, there was an estimated 2 (95% CI: -2 to 6) per 1000 more entacapone patients than placebo (carbidopa/levodopa) patients who experienced myocardial infarction in the double-blind wearing-off studies.

Adverse Reactions from Post-marketing Reports

The following are additional adverse drug reactions that have been reported since the introduction of entacapone for combination use with levodopa/DDC inhibitor. Adverse reactions are ranked under headings of frequency using the following convention: Very common (≥10%); common (≥1% to <10%); uncommon (≥0.1% to <1%); rare (≥0.01% to <0.1%); very rare (<0.01% including isolated reports).

Body as a whole

Very rare : weight decrease

Dermatological disorders:

Rare : erythematous or maculopapular rash

Very rare : urticaria, skin, hair, beard and nail discolourations

Gastrointestinal disorders

Very rare : anorexia, colitis

Hepatic disorders:

Very rare : hepatitis with cholestatic features

Psychiatric disorders:

Very rare : agitation

Isolated cases of neuroleptic malignant syndrome (NMS) have been reported, especially following abrupt reduction or discontinuation of entacapone and other dopaminergic medications.

Isolated cases of rhabdomyolysis have been reported.

Isolated cases of angiodema have been reported after initiation of Stalevo.

Other
The following adverse reactions have also been observed:

Gastrointestinal disorders
Common : dyspepsia

Musculoskeletal and connective tissue disorders
Very common : muscle, musculoskeletal and connective tissue pain
Common : arthralgia

Renal and urinary disorders
Common : urinary tract infection

Adverse Effects in Laboratory Tests
The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and entacapone.

Abnormalities include elevated values of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. Commonly, levels of blood urea nitrogen and uric acid are lower during administration of levodopa/carbidopa than with levodopa alone. Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported. Positive Coombs' tests have been reported, both for levodopa/carbidopa and for levodopa alone, but haemolytic anaemia is extremely rare.

Levodopa/carbidopa may cause false positive results 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.

Slight decreases in haemoglobin, erythrocyte count and haematocrit have been reported during entacapone treatment. The underlying mechanism may involve decreased absorption of iron from the gastrointestinal tract. During long-term (6 months) treatment with entacapone, a clinically significant decrease in haemoglobin has been observed in 1.8% of patients. A small number of reports of clinically significant increases in liver enzymes have been received.

DOSAGE AND ADMINISTRATION

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

Patients should be instructed to take only one Stalevo tablet per dose administration. The experience with total daily dosage greater than 200 mg carbidopa anhydrous is limited, whereas patients receiving less than 70-100 mg carbidopa anhydrous a day are more likely to experience nausea and vomiting. The maximum recommended daily dose of entacapone is 2000 mg, therefore the maximum Stalevo dose must not exceed 10 tablets per day, for the Stalevo strengths of 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, and 150/37.5/200 mg. Ten (10) tablets of Stalevo 150/37.5/200 mg equals 375 mg of carbidopa anhydrous a day. Therefore, using a maximum recommended daily dose of 375 mg of carbidopa anhydrous, 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.

Generally speaking, 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 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 one of the available Stalevo tablet strengths, 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, discontinue dosing of levodopa/benserazide the previous night and start Stalevo the next morning. Begin with a dosage of Stalevo that will provide either the same amount of levodopa or slightly (5-10 %) more.

How to Transfer Patients Taking Levodopa/DDC Inhibitor Preparations Not Currently Taking 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 and whose daily levodopa dose is above 800 mg (see Table 3). 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.

Table 3: The percentage of Parkinson's disease patients decreasing levodopa dose by 4-6 weeks after entacapone initiation as grouped by baseline levodopa dose and presence of dyskinesias (data from NOMECOMT, SEESAW, CELOMEN and UK-IRISH trials)

	Levodopa dose < 600 mg/day (n=180)	**Levodopa dose 600-800 mg/day (n=180)**	**Levodopa dose > 800 mg/day (n=180)**
Patients without dyskinesias	4%	21%	28%
Patients with dyskinesia	31%	43%	66%

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.

There are no data on transferring patients from controlled-release formulations of levodopa/carbidopa to Stalevo.

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 the above section. 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 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 anhydrous/ 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 (see 'PRECAUTIONS - Neuroleptic Malignant Syndrome and Rhabdomyolysis').

Children and Adolescents

Stalevo is not recommended for use in children below age 18 due to lack of data on safety and efficacy.

Elderly Patients

No dosage adjustment of Stalevo is required for elderly patients (see "PHARMACOLOGY – Pharmacokinetics in elderly patients").

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 "PHARMACOLOGY - Pharmacokinetics in patients with liver impairment").

Renal Impairment

Renal insufficiency 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 with severe renal impairments including those receiving dialysis therapy (see "PHARMACOLOGY - Pharmacokinetics in patients with renal impairment").

Method of Administration

Each tablet is to be taken orally either with or without food (see "PHARMACOLOGY-Pharmacokinetics"). One tablet contains one treatment dose and the tablet may only be administered as whole tablets.

OVERDOSAGE

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 therapy is similar to acute overdosage with levodopa. Pyridoxine, however, is not effective in reversing the actions of Stalevo. Hospitalisation is advised and general supportive measures should be employed with repeated doses of activated 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. Intravenous fluids should be administered judiciously and an adequate airway maintained. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmia. If required, appropriate, anti-arrhythmic therapy should be given. The possibility that the patient has taken other drugs in addition to Stalevo should be taken into consideration. The value of dialysis in the treatment of overdosage is not known.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Stalevo 50/12.5/200 are round, biconvex tablets marked with 'LCE 50' on one side
Stalevo 75/18.75/200 are oval tablets marked with 'LCE 75' on one side
Stalevo 100/25/200 are oval tablets marked with 'LCE 100' on one side
Stalevo 125/31.25/200 are oval tablets marked with 'LCE 125' on one side
Stalevo 150/37.5/200 are elongated-ellipse shaped tablets marked with 'LCE 150' on one side

Stalevo 200/50/200 are oval tablets marked with ‘LCE 200’ on one side

Stalevo strengths 50/12.5/200 mg, 100/25/200 mg and 150/37.5/200 mg are brownish- *or* greyish-red, film-coated tablets. Stalevo strength 200/50/200 mg is a dark brownish-red film-coated tablet. Stalevo strengths 75/18.75/200 mg and 125/31.25/200 mg are light brownish red, film-coated tablets. All strengths are registered in bottles of 10, 30 100 and 250* tablets.

* Stalevo 75/18.75/200 mg and 125/31.25/200 mg and 200/50/200 mg tablets are not available in bottles of 250 tablets.

Storage: Store below 30^{o}C. Keep out of the reach of children.

POISONS SCHEDULE OF THE MEDICINE

All active ingredients are Schedule 4.

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113

® = Registered Trademark

DATE OF MOST RECENT AMENDMENT

04 September 2013