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STALEVO™ LABELING

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STALEVO™ 50

STALEVO™ 100

STALEVO™ 150

(carbidopa, levodopa and entacapone) Tablets

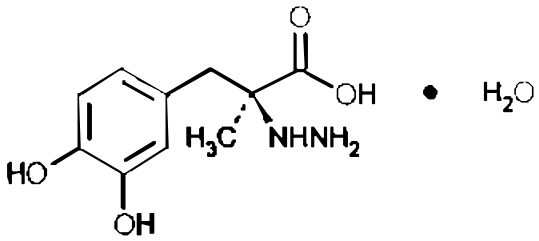
Rx only

Prescribing Information

DESCRIPTION

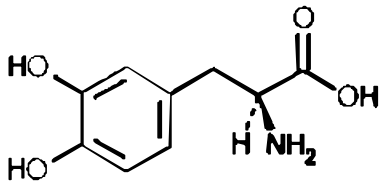
STALEVO™ (carbidopa, levodopa and entacapone) is a combination of carbidopa, levodopa and entacapone for the treatment of Parkinson's disease.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is



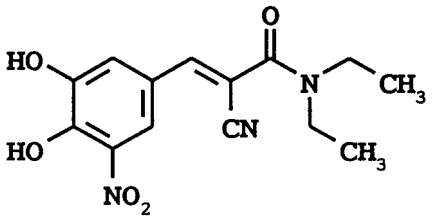
Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is



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Entacapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is a nitro-catechol-structured compound with a molecular weight of 305.3. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$ and its structural formula is



STALEVO™ (carbidopa, levodopa and entacapone) is supplied as tablets in three strengths:

STALEVO 50, containing 12.5mg of carbidopa, 50mg of levodopa and 200mg of entacapone

STALEVO 100, containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone

STALEVO 150, containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone

The inactive ingredients of the STALEVO tablet are corn starch, croscarmellose sodium, glycerol 85%, hypromellose, magnesium stearate, mannitol, polysorbate 80, povidone, sucrose, red iron oxide, titanium dioxide, and yellow iron oxide.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements.

Mechanism of Action

Levodopa

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Carbidopa

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to

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the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for transport to the brain. When coadministered with levodopa, carbidopa increases plasma levels of levodopa and reduces the amount of levodopa required to produce a given response by about 75 %. Carbidopa prolongs the plasma half-life of levodopa from 50 minutes to 1.5 hours and decreases plasma and urinary dopamine and its major metabolite, homovanillic acid. The t_{max} of levodopa, however, was unaffected by the coadministration.

Entacapone

Entacapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include DOPA, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

When entacapone is given in conjunction with levodopa and carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels may also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

When 200 mg entacapone is coadministered with levodopa/carbidopa, it increases levodopa plasma exposure (AUC) by 35-40% and prolongs its elimination half-life in Parkinson's disease patients from 1.3 to 2.4 hours. Plasma levels of the major COMT-mediated dopamine metabolite, 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD), are also markedly decreased proportionally with increasing dose of entacapone.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

Pharmacokinetics

The pharmacokinetics of Stalevo tablets have been studied in healthy subjects (age 45-75 years old). Overall, following administration of corresponding doses of levodopa, carbidopa and

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entacapone as STALEVO or as carbidopa/levodopa product plus Comtan® (entacapone) tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

Absorption/Distribution:
Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}.

The food-effect on the STALEVO tablet has not been evaluated.

Levodopa

The pharmacokinetic properties of levodopa following the administration of single dose STALEVO™ (carbidopa, levodopa and entacapone) tablets are summarized in Table 1.

Table 1. Pharmacokinetic characteristics of levodopa with different tablet strengths of STALEVO (mean ±SD)

Tablet strength	AUC_{0-} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)
12.5 - 50 - 200 mg	1040 ± 314	470 ± 154	1.1 ± 0.5
25 - 100 - 200 mg	2910 ± 715	975 ± 247	1.4 ± 0.6
37.5 - 150 - 200 mg	3770 ± 1120	1270 ± 329	1.5 ± 0.9

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa (see PRECAUTIONS).

Levodopa is bound to plasma protein only to a minor extent (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.

Carbidopa is approximately 36 % bound to plasma protein.

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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 of entacapone.

The plasma protein binding of entacapone is 98% over the concentration range of 0.4 - 50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism and Elimination:

Levodopa
The elimination half-life of levodopa, the active moiety of antiparkinsonian activity, was 1.7 hours (range 1.1-3.2 hours).

Levodopa is extensively metabolized to various metabolites. Two major pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa
The elimination half-life of carbidopa was on average 1.6 to 2 hours (range 0.7-4.0 hours).

Carbidopa is metabolized to two main metabolites (á-methyl-3-methoxy-4-hydroxyphenylpropionic acid and á-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone
The elimination half-life of entacapone was on average 0.8 to 1 hours (0.3-4.5 hours).

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the cis-isomer, the only active metabolite. Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates. The glucuronides account for 95 % of all urinary metabolites (70% as parent- & 25% as cis-isomer- glucuronides). The glucuronide conjugate of the cis-isomer is inactive. After oral administration of a 14C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

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

Special Populations:

Hepatic Impairment:

STALEVO™ (carbidopa, levodopa and entacapone)

While there are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment, STALEVO should be administered cautiously to patients with biliary obstruction or hepatic disease since biliary excretion appears to be the major route of excretion of entacapone and hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200mg entacapone was administered alone.

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/dopa decarboxylase inhibitor coadministration, 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.

Renal Impairment:

STALEVO™ (carbidopa, levodopa and entacapone):

STALEVO should be administered cautiously to patients with severe renal disease. There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment.

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 coadministration, 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).

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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.

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:
The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and/or 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.

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Drug Interactions: See PRECAUTIONS, Drug Interactions

Clinical Studies

Each STALEVO™ (carbidopa, levodopa and entacapone) tablet, provided in three single-dose strengths, contains carbidopa and levodopa in ratio 1:4 and a 200mg dose of entacapone. The three STALEVO tablet strengths have been shown to be bioequivalent to the corresponding doses of standard release carbidopa-levodopa 25-100mg tablets and Comtan 200mg tablets.

The effectiveness of entacapone as an adjunct to levodopa in the treatment of Parkinson's disease was established in three 24-week multicenter, randomized, double blind placebo-controlled trials in patients with Parkinson's disease. In two of these trials, the patients' disease was "fluctuating", i.e., was characterized by documented periods of "On" (periods of relatively good functioning) and "Off" (periods of relatively poor functioning), despite optimum levodopa therapy. There was also a withdrawal period following 6 months of treatment. In the third trial patients were not required to have been experiencing fluctuations. Prior to the controlled part of these trials, patients were stabilized on levodopa for 2 - 4 weeks.

There is limited experience of using entacapone in patients who do not experience fluctuations.

In the first two studies to be described, patients were randomized to receive placebo or entacapone 200mg administered concomitantly with each dose of carbidopa-levodopa (up to 10 times daily, but averaging 4-6 doses per day). The formal double-blind portion of both trials was 6 months long. Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. In one study, conducted in the Nordic countries, the primary outcome measure was the total mean time spent in the "On" state during an 18-hour diary recorded day (6 a.m. to midnight). In the other study, the primary outcome measure was the proportion of awake time spent over 24 hours in the "On" state.

In addition to the primary outcome measure, the amount of time spent in the "Off" state was evaluated, and patients were also evaluated by subparts of the Unified Parkinson's Disease Rating Scale (UPDRS), a frequently used multi-item rating scale intended to assess mentation (Part I), activities of daily living (Part II), motor function (Part III), complications of therapy (Part IV), and disease staging (Part V & VI); an investigator's and patient's global assessment of clinical condition, a 7-point subjective scale designed to assess global functioning in Parkinson's Disease; and the change in daily carbidopa-levodopa dose.

In one of the studies, 171 patients were randomized in 16 centers in Finland, Norway, Sweden, and Denmark (Nordic study), all of whom received concomitant levodopa plus dopa-decarboxylase inhibitor (either carbidopa-levodopa or benserazide-levodopa). In the second trial, 205 patients were randomized in 17 centers in North America (US and Canada); all patients received concomitant carbidopa-levodopa.

The following tables display the results of these two trials:

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Table 2. Nordic Study

	Baseline	Change from Baseline at Month 6*	p-value vs. placebo
Primary Measure from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "On"			
Placebo	9.2	+0.1	–
Entacapone	9.3	+1.5	<0.001
Duration of "On" time after first AM dose (hrs)			
Placebo	2.2	0.0	–
Entacapone	2.1	+0.2	<0.05
Secondary Measures from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	5.3	0.0	–
Entacapone	5.5	- 1.3	<0.001
Proportion of Awake Time "On" * (%)**			
Placebo	63.8	+0.6	–
Entacapone	62.7	+9.3	<0.001
Levodopa Total Daily Dose (mg)			
Placebo	705	+14	–
Entacapone	701	- 87	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.1	+0.1	–
Entacapone	6.2	- 0.4	<0.001
Other Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Investigator's Global (overall) % Improved**			
Placebo	–	28	–
Entacapone	–	56	<0.01
Patient's Global (overall) % Improved**			
Placebo	–	22	–
Entacapone	–	39	N.S.‡
UPDRS Total			
Placebo	37.4	-1.1	–
Entacapone	38.5	-4.8	<0.01
UPDRS Motor			
Placebo	24.6	-0.7	–
Entacapone	25.5	-3.3	<0.05
UPDRS ADL			
Placebo	11.0	-0.4	–
Entacapone	11.2	-1.8	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure

** At least one category change at endpoint.

*** Not an endpoint for this study but primary endpoint in the North American Study.

‡ Not significant.

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Table 3. North American Study

	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Primary Measure from Home Diary (for a 24-hour Diary Day)			
Percent of Awake Time "On"			
Placebo	60.8	+2.0	–
Entacapone	60.0	+6.7	<0.05
Secondary Measures from Home Diary (for a 24-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	6.6	- 0.3	–
Entacapone	6.8	- 1.2	<0.01
Hours of Awake Time "On"			
Placebo	10.3	+ 0.4	–
Entacapone	10.2	+ 1.0	N.S.‡
Levodopa Total Daily Dose (mg)			
Placebo	758	+ 19	–
Entacapone	804	- 93	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.0	+ 0.2	–
Entacapone	6.2	0.0	N.S.‡
Other Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Investigator's Global (overall) % Improved**			
Placebo	–	21	–
Entacapone	–	34	<0.05
Patient's Global (overall) % Improved**			
Placebo	–	20	–
Entacapone	–	31	<0.05
UPDRS Total***			
Placebo	35.6	+2.8	–
Entacapone	35.1	-0.6	<0.05
UPDRS Motor***			
Placebo	22.6	+1.2	–
Entacapone	22.0	-0.9	<0.05
UPDRS ADL***			
Placebo	11.7	+1.1	–
Entacapone	11.9	0.0	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure.

** At least one category change at endpoint.

*** Score change at endpoint similarly to the Nordic Study.

‡ Not significant.

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Effects on "On" time did not differ by age, sex, weight, disease severity at baseline, levodopa dose and concurrent treatment with dopamine agonists or selegiline.

Withdrawal of entacapone: In the North American study, abrupt withdrawal of entacapone, without alteration of the dose of carbidopa-levodopa, resulted in a significant worsening of fluctuations, compared to placebo. In some cases, symptoms were slightly worse than at baseline, but returned to approximately baseline severity within two weeks following levodopa dose increase on average by 80mg. In the Nordic study, similarly, a significant worsening of parkinsonian symptoms was observed after entacapone withdrawal, as assessed two weeks after drug withdrawal. At this phase, the symptoms were approximately at baseline severity following levodopa dose increase by about 50mg.

In the third placebo-controlled trial, a total of 301 patients were randomized in 32 centers in Germany and Austria. In this trial, as in the other two trials, entacapone 200mg was administered with each dose of levodopa/dopa decarboxylase inhibitor (up to 10 times daily) and UPDRS Parts II and III and total daily "On" time were the primary measures of effectiveness. The following results were seen for the primary measures, as well as for some secondary measures:

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Table 4. German-Austrian Study

	Primary Measures		
	Baseline	Change from Baseline at Month 6	p-value vs. placebo (LOCF)
UPDRS ADL*			
Placebo	12.0	+0.5	–
Entacapone	12.4	-0.4	<0.05
UPDRS Motor*			
Placebo	24.1	+0.1	–
Entacapone	24.9	-2.5	<0.05
Hours of Awake Time "On" (Home diary)**			
Placebo	10.1	+0.5	–
Entacapone	10.2	+1.1	N.S.‡
	Secondary Measures		
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
UPDRS Total*			
Placebo	37.7	+0.6	–
Entacapone	39.0	-3.4	<0.05
Percent of Awake Time "On" (Home diary)**			
Placebo	59.8	+3.5	–
Entacapone	62.0	+6.5	N.S.‡
Hours of Awake Time "Off" (Home diary)**			
Placebo	6.8	-0.6	–
Entacapone	6.3	-1.2	0.07
Levodopa Total Daily Dose (mg)*			
Placebo	572	+4	–
Entacapone	566	-35	N.S.‡
Frequency of Levodopa Daily Intake*			
Placebo	5.6	+0.2	–
Entacapone	5.4	0.0	<0.01
Global (overall) % Improved***			
Placebo	–	34	–
Entacapone	–	38	N.S.‡

* Total population; score change at endpoint.

** Fluctuating population, with 5-10 doses; score change at endpoint.

*** Total population; at least one category change at endpoint.

‡ Not significant.

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INDICATIONS

STALEVO™ (carbidopa, levodopa and entacapone) is indicated to treat patients with idiopathic Parkinson's disease:

1) To substitute (with equivalent strength of each of the three components) for immediate release cardidopa/levodopa and entacapone previously administered as individual products.

2) To replace immediate release carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" (only for patients taking a total daily dose of levodopa of 600mg or less and not experiencing dyskinesias, see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

STALEVO™ (carbidopa, levodopa and entacapone) tablets are contraindicated in patients who have demonstrated hypersensitivity to any component (carbidopa, levodopa, or entacapone) of the drug or its excipients.

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of entacapone and a non-selective MAO inhibitor (e.g., phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. As with carbidopa-levodopa, 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 manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl) (See PRECAUTIONS, Drug Interactions).

STALEVO is contraindicated in patients with narrow-angle glaucoma.

Because levodopa may activate malignant melanoma, STALEVO should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa as well as entacapone permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, e.g., dyskinesia (involuntary movements) may occur at lower dosages and sooner with levodopa preparations containing carbidopa and entacapone than with levodopa alone.

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The occurrence of dyskinesias may require dosage reduction (see PRECAUTIONS, Dyskinesia).

STALEVO™ (carbidopa, levodopa and entacapone) may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

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

As with levodopa, care should be exercised in administering STALEVO to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored carefully during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with STALEVO may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Neuroleptic Malignant Syndrome (NMS): Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of therapy with carbidopa-levodopa. Therefore, patients should be observed carefully when the dosage of STALEVO is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

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Drugs Metabolized By Catechol-*O*-Methyltransferase (COMT)

When a single 400mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine 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 epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol 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.

Ventricular tachycardia was noted in one 32-year-old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with STALEVO™ (carbidopa, levodopa and entacapone) provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Hypotension/Syncope

In the large controlled trials of entacapone, approximately 1.2% and 0.8% of 200mg entacapone and placebo patients treated also with levodopa/dopa decarboxylase inhibitor, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement).

Diarrhea

In clinical trials of entacapone, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200mg of entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor, respectively. In patients treated with entacapone, diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, 7 (1.2%) with mild and moderate diarrhea and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of

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entacapone. Two patients with diarrhea were hospitalized. Typically, diarrhea presents within 4 - 12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

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 200mg 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 200mg entacapone and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200mg 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 of withdrawal for dyskinesia were 1.5% and 0.8% for 200mg entacapone and placebo, respectively.

Other Events Reported With Dopaminergic Therapy

The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists.

Rhabdomyolysis: Cases of severe rhabdomyolysis have been reported with entacapone when used in combination with levodopa. The complicated nature of these cases makes it impossible to determine what role, if any, entacapone played in their pathogenesis. Severe prolonged motor activity including dyskinesia may account for rhabdomyolysis. One case, however, included fever and alteration of consciousness. It is therefore possible that the rhabdomyolysis may be a result of the syndrome described in Hyperpyrexia and Confusion (see PRECAUTIONS, Other Events Reported With Dopaminergic Therapy).

Hyperpyrexia and Confusion: Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. No cases have been reported following the abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing carbidopa,levodopa andentacapone combination treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with STALEVO, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This

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syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering entacapone has not been systematically evaluated.

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, nonergot derived drugs (e.g., 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.

Renal Toxicity

In a one-year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600mg) caused an increased incidence of nephrotoxicity in male rats that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

Hepatic Impairment

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, and DOSAGE AND ADMINISTRATION).

Biliary Obstruction

Caution should be exercised when administering STALEVO to patients with biliary obstruction, as entacapone is excreted mostly via the bile.

Information for Patients

The patient should be instructed to take STALEVO™ (carbidopa, levodopa and entacapone) only as prescribed. The patient should be informed that STALEVO is a standard-release formulation of carbidopa-levodopa combined with entacapone that is designed to begin release of ingredients within 30 minutes after ingestion. It is important that STALEVO be

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taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinsonian medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a “wearing-off” effect may occur at the end of the dosing interval. The physician should be notified for possible treatment-adjustments if such response poses a problem to patient's every-day life.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of STALEVO. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa, carbidopa-levodopa and STALEVO therapy.

NOTE: The suggested advice to patients being treated with STALEVO is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Hypotension may occur more frequently during initial therapy or when total daily levodopa dosage is increased. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with STALEVO.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on STALEVO to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with STALEVO.

Patients should be informed that nausea may occur, especially at the initiation of treatment with STALEVO.

Patients should be advised of the possibility of an increase in dyskinesia.

Carbidopa-levodopa combination and entacapone are known to affect embryo-fetal development in the rabbit and in the rat, respectively. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy).

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Carbidopa and entacapone are known to be excreted into maternal milk in rats. Because of the possibility that carbidopa, levodopa and entacapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of STALEVO than with levodopa.

STALEVO may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on carbidopa-levodopa therapy.

Entacapone is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreasing serum iron concentrations was noted in clinical trials. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after one year of treatment and there was no difference in rates of anemia or decreased hemoglobin levels.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with STALEVO™ (carbidopa, levodopa and entacapone).

Anti-hypertensive agents: Symptomatic postural hypotension has occurred when carbidopa-levodopa was added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with STALEVO is started, dosage adjustment of the antihypertensive drug may be required.

MAO inhibitors: For patients receiving nonselective MAO inhibitors, see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.

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Tricyclic antidepressants: There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa.

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid: Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa.

Phenytoin and papaverine: The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with carbidopa-levodopa should be carefully observed for loss of therapeutic response.

Iron salts: Iron salts may reduce the bioavailability of levodopa, carbidopa and entacapone. The clinical relevance is unclear.

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

Drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase (probenecid, cholestyramine, erythromycin, rifampicin, ampicillin and chloramphenicol): 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 (e.g., erythromycin, rifampicin, ampicillin and chloramphenicol).

Pyridoxine: STALEVO can be given to patients receiving supplemental pyridoxine. Oral coadministration of 10-25mg of pyridoxine 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 pyridoxine; therefore, STALEVO can be given to patients receiving supplemental pyridoxine.

Effect of levodopa & carbidopa in STALEVO on the metabolism of other drugs: Inhibition or induction effect of levodopa & carbidopa has not been investigated.

Effect of entacapone in STALEVO on the metabolism of other drugs: Entacapone is unlikely to inhibit the metabolism of other drugs that are metabolized by major P450s including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. In vitro studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A only at very high concentrations (IC50 from 200 to over 1000 µM; an oral 200mg dose achieves a highest level of approximately 5 µM in people); these enzymes would therefore not be expected to be inhibited in clinical use. However, no information is available regarding the induction effect from entacapone.

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Drugs that are highly protein bound (such as warfarin, salicylic acid, phenylbutazone, and diazepam)

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

Carbidopa
Carbidopa is approximately 36 % bound to plasma protein.

Entacapone

Entacapone is highly protein bound (98%). In vitro studies have shown no binding displacement between entacapone and other highly bound drugs, such as warfarin, salicylic acid, phenylbutazone, and diazepam.

Hormone levels

Of the ingredients in STALEVO, levodopa is known to depress prolactin secretion and increase growth hormone levels.

Carcinogenesis

In a two-year bioassay of carbidopa-levodopa, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Two-year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600mg). Mice were treated once daily by oral gavage with doses of 20, 100 or 600mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m^2 basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with carbidopa-levodopa has not been evaluated.

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Mutagenesis

Carbidopa was positive in the Ames test in the presence and absence of metabolic activation, was mutagenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the absence of metabolic activation, and was negative in the *in vivo* mouse micronucleus test.

Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with carbidopa-levodopa, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

Impairment of Fertility

In reproduction studies with carbidopa-levodopa, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Entacapone did not impair fertility or general reproductive performance in rats treated with up to 700mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD). Delayed mating, but no fertility impairment, was evident in female rats treated with 700mg/kg/day of entacapone.

Pregnancy

Pregnancy Category C. Carbidopa-levodopa caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa-levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa-levodopa to 20 times/10 times the maximum recommended human dose of carbidopa-levodopa. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximun recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. No teratogenic effects were observed in mice receiving up to 20 times the maximum recommended human dose of carbidopa-levodopa.

It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal.

In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000mg/kg/day in rats and 300mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of

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1600mg. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100mg/kg/day (plasma AUCs 0.4 times those in humans receiving the MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160mg/kg/day (plasma AUCs 7 times those in humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

There is no experience from clinical studies regarding the use of STALEVO in pregnant women. Therefore, STALEVO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In animal studies, carbidopa and entacapone were excreted into maternal rat milk. It is not known whether entacapone or carbidopa-levodopa are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when STALEVO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Carbidopa-levodopa

The most common adverse reactions reported with carbidopa-levodopa have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with carbidopa-levodopa:

Body as a Whole: Chest pain, asthenia.

Cardiovascular: Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

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Hypersensitivity: Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: Psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, increased libido. Convulsions also have occurred; however, a causal relationship with carbidopa-levodopa has not been established.

Respiratory: Dyspnea, upper respiratory infection.

Skin: Rash, increased sweating, alopecia, dark sweat.

Urogenital: Urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs' test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations, and may occur with STALEVO™ (carbidopa, levodopa and entacapone) are:

Body as a Whole: Abdominal pain and distress, fatigue.

Cardiovascular: Myocardial infarction.

Gastrointestinal: Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: Edema, weight gain, weight loss.

Musculoskeletal: Leg pain.

Nervous System/Psychiatric: Ataxia, extrapyramidal disorder, failing, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: Pharyngeal pain, cough.

Skin: Malignant melanoma (see also CONTRAINDICATIONS), flushing**.**

Special Senses: Oculogyric crisis, diplopia, blurred vision, dilated pupils.

Urogenital: Urinary retention, urinary incontinence, priapism.

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Miscellaneous: Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

Entacapone

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials of entacapone (N=1003) associated with the use of entacapone alone and not seen at an equivalent frequency among the placebo-treated patients were: dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Approximately 14% of the 603 patients given entacapone in the double blind, placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order are: psychiatric reasons (2% vs. 1%), diarrhea (2% vs. 0%), dyskinesia/hyperkinesia (2% vs. 1%), nausea (2% vs. 1%), abdominal pain (1% vs. 0%), and aggravation of Parkinson's disease symptoms (1% vs. 1%).

Adverse Event Incidence in Controlled Clinical Studies of Entacapone

Table 6 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to carbidopa-levodopa (or benserazide-levodopa).

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Table 5. Summary of Patients with Adverse Events after Start of Trial Drug Administration. At least 1% in Entacapone Group and > Placebo

SYSTEM ORGAN CLASS Preferred term	Entacapone (n = 603) % of patients	Placebo (n = 400)) % of patients
SKIN AND APPENDAGES DISORDERS		
Sweating increased	2	1
MUSCULOSKELETAL SYSTEM DISORDERS		
Back pain	2	1
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dyskinesia	25	15
Hyperkinesia	10	5
Hypokinesia	9	8
Dizziness	8	6
SPECIAL SENSES, OTHER DISORDERS		
Taste Perversion	1	0
PSYCHIATRIC DISORDERS		
Anxiety	2	1
Somnolence	2	0
Agitation	1	0
GASTROINTESTINAL SYSTEM DISORDERS		
Nausea	14	8
Diarrhea	10	4
Abdominal Pain	8	4
Constipation	6	4
Vomiting	4	1
Mouth dry	3	0
Dyspepsia	2	1
Flatulence	2	0
Gastritis	1	0
Gastrointestinal Disorders nos	1	0
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	3	1
PLATELET, BLEEDING & CLOTTING DISORDERS		
Purpura	2	1
URINARY SYSTEM DISORDERS		
Urine Discoloration	10	0
BODY AS A WHOLE - GENERAL DISORDERS		
Back Pain	4	2
Fatigue	6	4
Asthenia	2	1
RESISTANCE MECHANISM DISORDERS		
Infection Bacterial	1	0

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The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

Effects of gender and age on adverse reactions

No differences were noted in the rate of adverse events attributable to entacapone alone by age or gender.

DRUG ABUSE AND DEPENDENCE

Controlled substance class- STALEVO™ (carbidopa, levodopa and entacapone) is not a controlled substance.

Physical and psychological dependence- STALEVO has not been systematically studied, in animal or humans, for its potential for abuse, tolerance or physical dependence. In premarketing clinical experience, carbidopa-levodopa did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse and dependence of medications containing levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve an euphoric state.

OVERDOSAGE

Management of acute overdosage with STALEVO™ (carbidopa, levodopa and entacapone) is the same as management of acute overdosage with levodopa and entacapone. Pyridoxine is not effective in reversing the actions of STALEVO.

Hospitalization is advised, and general supportive measures should be employed, along 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. Intravenous fluids should be administered judiciously and an adequate airway maintained.

The adequacy of the respiratory, circulatory and renal systems should be carefully monitored and appropriate supportive measures employed. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known. Hemodialysis or hemoperfusion is unlikely to reduce entacapone levels due to its high binding to plasma proteins.

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There are very few cases of overdosage with levodopa reported in the published literature. Based on the limited available information, the acute symptoms of levodopa/dopa decarboxylase inhibitor overdosage can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g. hypotension, tachycardia) and more severe psychiatric problems at higher doses. An isolated report of rhabdomyolysis and another of transient renal insufficiency suggest that levodopa overdosage may give rise to systemic complications, secondary to dopaminergic overstimulation.

There have been no reported cases of either accidental or intentional overdose with entacapone tablets. However, COMT inhibition by entacapone treatment is dose-dependent. A massive overdose of entacapone may theoretically produce a 100% inhibition of the COMT enzyme in people, thereby preventing the O-methylation of endogenous and exogenous catechols.

The highest single dose of entacapone administered to humans was 800mg, resulting in a plasma concentration of 14.1 µg/mL. The highest daily dose given to humans was 2400mg, administered in one study as 400mg six times daily with carbidopa-levodopa for 14 days in 15 Parkinson's disease patients, and in another study as 800mg t.i.d. for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0 µg/mL (at 45 min., compared to 1.0 and 1.2 µg/mL with 200mg entacapone at 45 min.). Abdominal pain and loose stools were the most commonly observed adverse events during this study. Daily doses as high as 2000mg entacapone have been administered as 200mg 10 times daily with carbidopa-levodopa or benserazide-levodopa for at least 1 year in 10 patients, for at least 2 years in 8 patients and for at least 3 years in 7 patients. Overall, however, clinical experience with daily doses above 1600mg is limited.

The range of lethal plasma concentrations of entacapone based on animal data was 80 - 130 µg/mL in mice. Respiratory difficulties, ataxia, hypoactivity, and convulsions were observed in mice after high oral (gavage) doses.

DOSAGE AND ADMINISTRATION

Individual tablets should not be fractionated and only one tablet should be administered at each dosing interval.

Generally speaking, STALEVO should be used as a substitute for patients already stabilized on equivalent doses of carbidopa-levodopa and entacapone. However, some patients who have been stabilized on a given dose of carbidopa/levodopa may be treated with STALEVO if a decision has been made to add entacapone (see below).

The optimum daily dosage of STALEVO™ (carbidopa, levodopa and entacapone) must be determined by careful titration in each patient. STALEVO tablets are available in three strengths, each in a 1:4 ratio of carbidopa to levodopa and combined with 200mg of entacapone in a standard release formulation (STALEVO 50 containing 12.5mg of carbidopa,

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50mg of levodopa and 200mg of entacapone; STALEVO 100 containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone; and STALEVO 150 containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone).

Therapy should be individualized and adjusted according to the desired therapeutic response.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200mg is limited.

Clinical experience with daily doses above 1600mg of entacapone is limited. It is recommended that no more than one STALEVO tablet be taken at each dosing administration. Thus the maximum recommended daily dose of STALEVO is eight tablets per day.

How to transfer patients taking carbidopa-levodopa preparations and Comtan® (entacapone) tablets to STALEVO™ (carbidopa, levodopa and entacapone) tablets

There is no experience in transferring patients currently treated with formulations of carbidopa-levodopa other than immediate release carbidopa-levodopa with a 1:4 ratio (controlled release formulations, or standard release presentations with a 1:10 ratio of carbidopa-levodopa) and entacapone to STALEVO.

Patients who are currently treated with Comtan 200mg tablet with each dose of standard release carbidopa-levodopa, can be directly switched to the corresponding strength of STALEVO containing the same amounts of levodopa and carbidopa. For example, patients receiving one tablet of standard release carbidopa-levodopa 25/100mg and one tablet of Comtan 200mg at each administration can be switched to a single STALEVO 100 tablet (containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone).

How to transfer patients not currently treated with Comtan® (entacapone) tablets from carbidopa-levodopa to STALEVO™ (carbidopa, levodopa and entacapone) tablets

In patients with Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off" on their current standard release carbidopa-levodopa treatment, clinical experience shows that patients with a history of moderate or severe dyskinesias or taking more than 600mg of levodopa per day are likely to require a reduction in daily levodopa dose when entacapone is added to their treatment. Since dose adjustment of the individual components is impossible with fixed dose products, it is recommended that patients first be titrated individually with a carbidopa-levodopa product (ratio 1:4) and an entacapone product, and then transferred to a corresponding dose of STALEVO once the patient's status has stabilized.

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In patients who take a total daily levodopa dose up to 600mg, and who do not have dyskinesias, an attempt can be made to transfer to the corresponding daily dose of STALEVO. Even in these patients, a reduction of carbidopa-levodopa or entacapone may be necessary however, and the provider is reminded that this may not be possible with STALEVO. Since entacapone prolongs and enhances the effects of levodopa, therapy should be individualized and adjusted if necessary according to the desired therapeutic response.

Maintenance of STALEVO treatment

Therapy should be individualized and adjusted for each patient according to the desired therapeutic response.

When less levodopa is required, the total daily dosage of carbidopa-levodopa should be reduced by either decreasing the strength of STALEVO at each administration or by decreasing the frequency of administration by extending the time between doses.

When more levodopa is required, the next higher strength of STALEVO should be taken and/or the frequency of doses should be increased, up to a maximum of 8 times daily and not to exceed the maximum daily dose recommendations as outlined above.

Addition of Other Antiparkinsonian Medications

Standard drugs for Parkinson's disease may be used concomitantly while STALEVO is being administered, although dosage adjustments may be required.

Interruption of Therapy

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of levodopa preparations. Patients should be observed carefully if abrupt reduction or discontinuation of STALEVO is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

If general anesthesia is required, STALEVO may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Special populations

Patients With Impaired Hepatic Function:

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease, compared to controls. However, these studies were conducted with single-dose entacapone without levodopa/dopa decarboxylase inhibitor coadministration, and therefore the effects of liver disease on the kinetics of chronically administered entacapone have not been evaluated (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone).

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HOW SUPPLIED

STALEVO™ (carbidopa, levodopa and entacapone) is supplied as film-coated tablets for oral administration in the following three strengths:

STALEVO 50 film-coated tablets containing 12.5mg of carbidopa, 50mg of levodopa and 200mg of entacapone.
The round, bi-convex shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 50" on one side.
HDPE bottle of 100 tablets……NDC 0078-0407-05
HDPE bottle of 250 tablets……NDC 0078-0407-28

STALEVO 100 film-coated tablets containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone.
The oval-shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 100" on one side.
HDPE bottle of 100 tablets……NDC 0078-0408-05
HDPE bottle of 250 tablets……NDC 0078-0408-28

STALEVO 150 film-coated tablets containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone
The elongated-ellipse shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 150" on one side.
HDPE bottle of 100 tablets……NDC 0078-0409-05
HDPE bottle of 250 tablets……NDC 0078-0409-28

Store at 25°C (77°F) excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature.]

STALEVO™ (carbidopa, levodopa and entacapone) tablets are manufactured by Orion Corporation, Orion Pharma (Espoo, Finland) and marketed by Novartis Pharmaceuticals Corporation (East Hanover, N.J. 07936, U.S.A.).

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