PRODUCT MONOGRAPH

[Pr]AURO-ENTACAPONE

Entacapone Tablets

200 mg

House Standard

Adjunct to levodopa and DDC inhibitor / COMT-Inhibitor

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THERAPEUTIC CLASSIFICATION

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ACTION AND CLINICAL PHARMACOLOGY

Entacapone is a reversible, selective and mainly peripherally acting inhibitor of catechol-O-methyltransferase (COMT). Entacapone has no antiparkinsonian effect of its own and is designed for concomitant administration with levodopa preparations.

COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a cathecol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. In the presence of a dopa decarboxylase (DDC) inhibitor, COMT becomes the major enzyme which is responsible for the metabolism of levodopa to 3-methoxy-4-hydroxy-l-phenylalanine (3-OMD).

The mechanism of action of entacapone is believed to be related to its ability to inhibit COMT and thereby alter the plasma pharmacokinetics of levodopa. When administered with levodopa and a DDC inhibitor (carbidopa or benserazide), entacapone decreases the degradation of levodopa in the peripheral tissues further by inhibiting the metabolism of levodopa to 3-OMD through the COMT pathway. This leads to more sustained plasma concentrations of levodopa. 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 also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

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.

PHARMACODYNAMICS

Effect of Entacapone on erythrocyte COMT activity

Studies in healthy volunteers and patients with Parkinson's disease have shown that entacapone dose-dependently and reversibly inhibits human erythrocyte COMT activity after oral administration. Following single doses of 200 and 800 mg of entacapone, maximal inhibition of erythrocyte COMT activity was 64% and 82%, respectively.

Effect of entacapone on the pharmacokinetics of levodopa and its metabolites

When 200 mg entacapone is administered together with levodopa/carbidopa, it increases the area under the curve (AUC) of levodopa by approximately 35% and the elimination half-life of levodopa is prolonged from 1.3 h to 2.4 h. In general, the average peak levodopa plasma concentration and the time of its occurrence (T_{max} of 1 hour) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment.

In a dose-response study in patients with Parkinson's disease, the maximal effect was obtained with a single dose of 200 mg entacapone. Doses of entacapone greater than 200 mg did not further improve the bioavailability of levodopa.

Studies in healthy volunteers and in patients with Parkinson's disease show that entacapone dose-dependently decreases the formation of 3-OMD from levodopa. The chronic use of entacapone (200 mg, 3 to 10 times daily) in patients with Parkinson's disease, decreases the AUC of 3-OMD by 42 to 61%.

PHARMACOKINETICS AND METABOLISM OF ENTACAPONE

Entacapone pharmacokinetics are linear over a dose range of 5 to 200 mg. A slight non linearity in AUC was seen at doses greater than or equal to 400 mg in a single dose, dose-response, study in patients with Parkinson's disease. The pharmacokinetics of entacapone are independent of levodopa/DDC coadministration.

Absorption

There are large intra- and interindividual variations in the absorption of entacapone.

Entacapone is rapidly absorbed from the GI tract, reaching peak concentrations (Cmax) in the plasma in approximately one hour. The drug has an extensive first-pass metabolism with bioavailability of about 35% following oral administration of a 200 mg dose. Cmax, after a single 200 mg dose of entacapone, is approximately 1.2 µg/mL. Food does not affect the absorption of entacapone to any significant extent.

Distribution and protein binding

The volume of distribution of entacapone at steady state after i.v. injection is small (20L). Entacapone does not distribute widely into tissues due to its high plasma protein binding. Based on *in vitro* studies, the plasma protein binding of entacapone is 98% over the concentration range of 0.4 to 50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism/Elimination

Entacapone undergoes extensive metabolism, mainly in the liver. The main metabolic pathway of entacapone in humans is the isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer; the glucuronide conjugate is inactive.

The elimination of entacapone occurs mainly by non-renal metabolic pathways. It is estimated that 80-90% of the dose is excreted in feces, although this has not been confirmed in man. Approximately 10-20% is excreted in urine. Only traces of entacapone are found as unchanged drug in urine. The major part (95 %) of the drug excreted in urine is conjugated with glucuronic acid. Of the metabolites found in urine only about 1 % have been formed through oxidation.

The total body clearance of entacapone, after i.v. administration, is about 800 mL/min. It is eliminated with a short elimination half-life; the half-life for ß-phase being about 0.5 hours and for the γ-phase about 2.5 hours. The ß-phase is predominant, and the γ-phase accounts for approximately 8 % of the plasma-time-concentration curve (AUC) following i.v. administration.

Hepatic Impairment

The metabolism of the drug is slowed in patients with mild to moderate (Child-Pugh grading Class A and B) hepatic impairment caused by cirrhotic disease. In these patients, the AUC and Cmax values were approximately two-fold greater than those in demographically-matched healthy volunteers. As there are no clinical trial data to establish a safe and effective dosing regimen for hepatically impaired patients, entacapone should be not be administered to patients with hepatic impairment (see **CONTRAINDICATIONS**).

Renal Impairment

The pharmacokinetics of entacapone were evaluated in healthy volunteers and in patients with moderately (Clcr 0.60 - 0.89 mL/sec/1.73 m^2) and severely (Clcr 0.20 - 0.44 mL/sec/1.73 m^2) impaired renal function. After a single oral dose of 200 mg, the pharmacokinetics of entacapone were not significantly changed in patients with moderate to severe renal impairment.

Age, gender and race

Entacapone pharmacokinetics are independent of age. No formal gender studies have been conducted. Racial representation in clinical trials was largely limited to Caucasians (there were only 4 blacks in one US trial and no Asians in any of the clinical trials); no conclusions can therefore be reached about the effect of entacapone on groups other than Caucasian.

Studies Assessing Potential Drug Interactions

Effect of entacapone on the metabolism of other drugs

Protein binding: Entacapone is highly protein bound (98%). *In vitro* studies have shown that entacapone, at therapeutic concentrations, does not displace drugs of which a large proportion is bound to plasma proteins (e.g. warfarin, salicylic acid, phenylbutazone, and diazepam). On the other hand, entacapone is not markedly displaced by any of these drugs at therapeutic concentrations.

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of Auro-Entacapone Tablets 200 mg (Test) of Aurobindo Pharma Limited, India manufactured for Auro Pharma Inc. (Canada) and Comtan® (Entacapone) Tablets 200 mg (Reference) of Novartis Pharmaceuticals Canada Inc., (Canada) was conducted in 43 healthy, adult, male subjects under fasting conditions.

Summary Table of the Comparative Bio-availability Data

Entacapone (1 x 200 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{0\rightarrow t}$ (hr.µg/mL)	2355.2 2544.6 (47.1)	2363.0 2534.8 (41.5)	99.7	92.9 -107.0
$AUC_{0\rightarrow\infty}$ (hr.µg/mL)	2390.9 2579.2 (46.7)	2401.7 2575.4 (46.7)	99.5	92.9 – 106.7
C_{max} (µg/mL)	1879.1 2215.8 (65.2)	1710.3 2049.9 (69.6)	109.9	92.8 – 130.1
T_{max}§ (h)	0.7 (0.3 - 4.0)	1.0 (0.3 – 5.0)		
$T_{½}$$ (h)	1.3 (62.3)	1.5 (89.8)		

*AURO-ENTACAPONE (Entacapone) Tablets 200 mg, by Auro Pharma Inc.
† COMTAN (Entacapone) Tablets 200 mg, of Novartis Pharmaceuticals Canada Inc., (Canada) were purchased from Canada.
§ Expressed as the median (range) only.
$ Expressed as arithmetic mean (%CV) only.

The effectiveness of entacapone as an adjunct to levodopa/ DDC therapy in the treatment of Parkinson's disease was demonstrated in three separate 24-week randomized, placebo-controlled, double-blind, multicenter studies in 676 patients with mild to moderate Parkinson's disease (average Hoen and Yahr score: 1.5-3) . In two of these studies (Nordic Study and North American "SEESAW" Study), the patients' disease was "fluctuating", i.e. was characterized by documented periods of "On" (periods with relatively good functioning) and "Off" (periods of relatively poor functioning), despite optimum levodopa therapy. In the third trial (German-Austrian "CELOMEN" Study) patients were not required to have been experiencing fluctuations. On average the patients evaluated had been treated with levodopa/ DDC inhibitor therapy for 8.3 years and 86 % were treated with other antiparkinsonian medication (dopamine agonists, selegiline, amantadine, anticholinergics) in addition to a levodopa/DDC inhibitor.

In the two studies in patients with Parkinson's disease with documented episodes of end-of-dose motor fluctuations despite optimal levodopa therapy, patients were randomized to receive placebo (n=188) or 200 mg entacapone (n=188) with each daily dose of levodopa/DDC inhibitor (carbidopa or benserazide; average 4 -to- 6 doses per day). The formal double-blind portion of both trials was 6 months. Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. In the Nordic Study the primary outcome measure was the total mean time spent in the "On" state during an 18-hour diary recorded day, in the North American "SEESAW" 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, as secondary measures, the amount of time spent in the "Off" state was evaluated and patients were also evaluated in subparts of the Unified Parkinson's Disease Rating Scale (UPDRS), an investigator's and patients' global assessment of clinical condition, a 7-point subjective scale designed to assess global functioning in Parkinson's Disease and for change in daily levodopa/DDC dose. Results for the primary efficacy measure for these two studies are shown in Table 1.

TABLE 1: Primary Outcome Measures: Hours of awake time "On" (Nordic Study) ; Percent of Awake time "On" (North American "SEESAW" study)

Nordic Study			
	Placebo (n=86) Mean (± SD)	Entacapone (n=85) Mean (± SD)	Difference
Baseline*	9.2 ± 2.5	9.3 ± 2.2	
Week 8-24*†	9.4 ± 2.6	10.7 ± 2.2	1h 20 min (8.3%) $CI_{95\%}$ 45 min, 1h 56 min
North American "SEESAW" Study			
	Placebo (n=102)	Entacapone (n=103)	Difference
Baseline**	60.8 ±14.0	60.0 ±15.2	
Week 8-24**‡	62.8 ±16.8	66.8 ± 14.5	4.5% (0 h 35 min) $CI_{95\%}$ 0.93%, 7.97%

* daily ON time (h); † Values represent the average of weeks 8, 16 and 24, by protocol-defined outcome measure.
** Proportion ON time %; ‡Values represent the average of weeks 8, 16 and 24, by protocol defined outcome measure.

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

Corresponding significant decreases in OFF time were also noted. Change from baseline in hours of awake time AOff A in the Nordic Study were: -1.3 hours for the entacapone group; 0 hours for the placebo group and in the North American "SEESAW" Study were: -1.2 hours for the entacapone group; ¯0.3 for the placebo group.

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

In the third placebo controlled trial (Austrian-German "CELOMEN" Study), as in the other two trials, patients were randomized to receive 200 mg entacapone or placebo with each dose of levodopa/DDC inhibitor (up to 10 times daily). The CELOMEN study was primarily designed as a safety trial. Measures of effectiveness in this study were the UPDRS Parts II and III and total daily "On" time (see Table 2).

TABLE 2: Outcome Measures: UPDRS and Hours of awake time "On" (Austrian-German "CELOMEN" Study)

UPDRS ADL*			
	Placebo (n =104) Mean (± SD)	Entacapone (n =191) Mean (±SD)	Difference
Baseline	12.0 ± 5.8	12.4 ± 6.1	
Week 24	12.4 ± 6.5	11.1 ± 6.3	-1.35 CI_{95} -2.54, -0.16
UPDRS MOTOR*			
	Placebo (n = 102)	Entacapone (n = 190)	Difference
Baseline	24.1 ± 12.1	24.9 ± 12.9	
Week 24	24.3 ± 12.9	21.7 ± 12.1	-2.83 CI_{95} -4.95, -0.71
Hours of Awake Time "On" (Home diary)**			
	Placebo (n =60)	Entacapone (n =114)	Difference
Baseline	10.1 ± 2.5	10.2 ± 2.6	
Week 24	10.6 ± 3.0	11.8 ± 2.7	1.08 CI_{95} 0.13, 2.03

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

INDICATIONS AND CLINICAL USE

AURO-ENTACAPONE (entacapone) is indicated as an adjunct to levodopa/carbidopa or levodopa/ benserazide preparations to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (see CLINICAL PHARMACOLOGY: Clinical Trials).

Entacapone's effectiveness has not been systematically evaluated in patient's with idiopathic Parkinson's Disease who do not experience end-of-dose "wearing-off".

Since AURO-ENTACAPONE is to be used in combination with a levodopa/DDC inhibitor, the complete prescribing information for levodopa/carbidopa and levodopa/benserazide are also applicable when AURO-ENTACAPONE is added to the treatment regimen.

CONTRAINDICATIONS

- AURO-ENTACAPONE (entacapone) is contraindicated in patients with known hypersensitivity to entacapone or to any of the excipients (see PHARMACEUTICAL INFORMATION – Composition for a complete listing).
- AURO-ENTACAPONE is contraindicated in patients with hepatic impairment.
- AURO-ENTACAPONE should not be given concomitantly with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of selective MAO-A and selective MAO-B inhibitors is equivalent to non-selective MAO-inhibition, therefore, they should not both be given concomitantly with AURO-ENTACAPONE and levodopa preparations. Non-selective MAO inhibitors must be discontinued at least two weeks prior to initiating therapy with entacapone. Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegiline 10 mg/day) when co-administered with AURO-ENTACAPONE and levodopa (see **PRECAUTIONS**, **Drug Interactions**, Selegiline).
- AURO-ENTACAPONE should not be given to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, pulmonary (including bronchial asthma), or renal disease.
- AURO-ENTACAPONE is contraindicated in patients with a previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.
- AURO-ENTACAPONE should not be given when administration of a sympathomimetic amine is contraindicated.
- AURO-ENTACAPONE is contraindicated in patients with pheochromocytoma due to the increased risk of hypertensive crisis.
- AURO-ENTACAPONE should not be given to patients with narrow angle glaucoma.
- Because levodopa may activate a malignant melanoma, AURO-ENTACAPONE should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

Sudden Onset of Sleep

Patients receiving treatment with entacapone in combination with levodopa/DDC inhibitor and/or other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including the driving of a car, which sometimes resulted in accidents. Although some of the patients reported somnolence while treated with levodopa/DDC inhibitor and entacapone, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with AURO-ENTACAPONE used in combination with levodopa/decarboxylase DDC inhibitor, such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking AURO-ENTACAPONE in combination with levodopa/decarboxylase DDC inhibitor. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician (see PRECAUTIONS-Information for Patients).

Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Currently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

Skin

Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. For the reasons stated above, patients and healthcare providers are advised to monitor for melanomas frequently and on a regular basis when using AURO-ENTACAPONE for *any* indication (see PRECAUTIONS-Information for Patients). Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Prostate Cancer

Prostate cancer has been reported in elderly males during the use of entacapone in combination with levodopa/carbidopa in clinical trials. The clinical relevance of these adverse events is not known (see ADVERSE REACTIONS). Physicians are advised to adhere to the routine examination schedule for all male patients for symptoms and risk factors of prostate cancer including evaluation prior to initiating treatment with AURO-ENTACAPONE. Physicians should emphasize to patients the importance of adhering to routine examinations for prostate cancer during extended treatment with entacapone (see PRECAUTIONS-Information for Patients).

Drugs metabolized by Catechol-O-methyltransferase (COMT)

When a single 400 mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/DDC 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 a 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.

Abnormal Weight Decrease

In isolated cases, combined progressive anorexia, asthenia and weight decrease within a relatively short period of time have been reported prior to elevations in liver enzymes and serious hepatic adverse events. For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including assessment of liver function should be considered (See PRECAUTIONS – Diarrhea and Weight Decrease).

Cardiovascular

Myocardial infarction and other ischemic heart disease events have been reported with the use of entacapone in combination with levodopa/DDC inhibitor in clinical trials (see ADVERSE REACTIONS). Entacapone therapy should be administered with caution to patients with ischemic heart disease or risk factors for cardiovascular disease.

In patients with a history of myocardial infarction or who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments in a facility with provisions for intensive cardiac care.

Periodic evaluation of cardiovascular function is recommended during extended therapy with entacapone.

PRECAUTIONS

General

Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended during extended therapy with levodopa/DDC inhibitor and AURO-ENTACAPONE (entacapone).

AURO-ENTACAPONE enhances the effects of levodopa. Therefore, to reduce levodopa-related dopaminergic adverse reactions, e.g. dyskinesias, nausea, vomiting and hallucinations, it may be necessary to adjust the levodopa dosage within the first days to first weeks following the initiation of AURO-ENTACAPONE treatment.

AURO-ENTACAPONE has no antiparkinsonian effect of its own and therefore should only be used as an adjunct to levodopa/carbidopa or levodopa/benserazide treatment. The warnings and precautions given for levodopa/carbidopa and levodopa/benserazide treatment should therefore be taken into account when AURO-ENTACAPONE is used.

If AURO-ENTACAPONE treatment is discontinued, it is necessary to adjust the dosing of other parkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see DOSAGE AND ADMINISTRATION).

Neuroleptic Malignant Syndrome

A symptom complex resembling the neuroleptic malignant syndrome (NMS), characterized by elevated temperature, muscular rigidity, altered consciousness (e.g., agitation, confusion, coma), autonomic instability (tachycardia, labile blood pressure) and elevated CPK has been reported in association with the rapid dose reduction, or withdrawal of, or changes in antiparkinsonian therapy. In individual cases, only some of these symptoms and/or findings may be evident. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity.

Cases with similar signs and symptoms have been reported in association with entacapone therapy, especially following abrupt reduction or discontinuation of entacapone and other dopaminergic medications. The complicated nature of these cases makes it difficult to determine what role, if any, entacapone may have played in their pathogenesis. No cases have been reported following abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing entacapone treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with AURO-ENTACAPONE, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. If signs and/or symptoms occur despite a

slow withdrawal of entacapone, an increase in levodopa dosage may be necessary. Tapering entacapone has not been systematically evaluated.

Rhabdomyolysis

Rhabdomyolysis secondary to severe dyskinesias or Neuroleptic Malignant Syndrome (NMS) has been observed rarely in patients with Parkinson's disease. Very rare cases of rhabdomyolysis have been reported with entacapone treatment.

Symptoms associated with rhabdomyolysis can include muscle pain, muscle tenderness and weakness, bruising, elevated temperature, urinary retention, confusion, and elevated CPK. Acute renal failure is serious complication associated rhabdomyolysis and has been reported in some cases of rhabdomyolysis that have occurred during entacapone treatment.

Orthostatic Hypotension/Syncope

AURO-ENTACAPONE may aggravate levodopa-induced orthostatic hypotension. AURO-ENTACAPONE should be given with caution to patients who are treated with drugs which may cause orthostatic hypotension. In controlled clinical trials approximately 1.2% of patients who received 200 mg entacapone and 0.8% of patients treated with placebo 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.

Diarrhea and Weight Decrease

In clinical trials, diarrhea was reported as an adverse event in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg entacapone and placebo, respectively. In patients treated with entacapone diarrhea was generally mild to moderate in severity (8.6%) but was reported as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients (1.2% with mild to moderate diarrhea and 0.3% with severe diarrhea). Diarrhea generally resolved after discontinuation of entacapone. Two patients with diarrhea required hospitalization. Typically, diarrhea presents within 4 to 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. For patients experiencing diarrhea, close monitoring of weight is recommended in order to assess the need for treatment discontinuation to avoid excessive weight loss (see also WARNINGS-Abnormal Weight Decrease).

Colitis

Some patients who experienced diarrhea and weight loss during entacapone treatment were subsequently diagnosed with colitis, following colonoscopy and biopsy (See ADVERSE REACTIONS-Post Introduction Reports). Prolonged or persistent diarrhea suspected to be related to entacapone may be a sign of colitis. In the event of prolonged or persistent diarrhea, entacapone should be discontinued and appropriate medical therapy and investigations considered.

Dyskinesia

AURO-ENTACAPONE may potentiate the dopaminergic side effects of levodopa and may 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 200 mg entacapone and placebo, respectively.

Psychiatric

Levodopa may cause mental disturbances. All patients treated with levodopa/DDC inhibitor in combination with AURO-ENTACAPONE should be monitored carefully for the development of mental changes (e.g. hallucinations and psychoses), depression with suicidal tendencies, and serious antisocial behaviour. Patients with past or current psychosis should be treated with caution.

Behavioral Changes: Patients and caregivers should be advised to adhere to dosage instructions given by the physician. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioral symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as entacapone in association with levodopa. Safety data from various sources including literature, clinical trials, and post-market analysis have described an addictive pattern of dopamine replacement therapy, in which patients use doses in excess of those required to control their motor symptoms. Because patients may not recognize these behaviors as abnormal, it is important for physicians to specifically ask patients and caregivers to identify new behavior patterns. Review of treatment is recommended if such symptoms develop. These symptoms were generally reversible upon dose reduction or treatment discontinuation (see ADVERSE REACTIONS).

Hallucinations: Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials, hallucinations developed in approximately 4% of patients treated with 200 mg entacapone or placebo. 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 hospitalization in 1.0% and 0.3% of patients in the 200 mg entacapone and placebo groups, 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, it is unknown whether other, non-ergot derived drugs (e.g., entacapone) that increase dopaminergic activity can cause them. 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 to 17 months.

Urine, Sweat and Saliva Discolouration

AURO-ENTACAPONE may cause a harmless intensification in the color of the patient's urine to brownish-orange. AURO-ENTACAPONE may also cause darkening of sweat and saliva.

Occupational Hazards: Psychomotor Performance

AURO-ENTACAPONE together with levodopa may cause dizziness and symptomatic orthostatism. Therefore, patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

AURO-ENTACAPONE in association with levodopa may have major influence on the ability to drive and use machines. Patients being treated with entacapone in association with levodopa and presenting with somnolence and/or sudden sleep onset episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes have resolved (see WARNINGS, Sudden Onset of Sleep).

Special Populations

Hepatic Impairment

The metabolism of entacapone is slowed in patients with mild to moderate (Child-Pugh grading Class A and B) hepatic impairment caused by cirrhotic disease. In these patients, the AUC and Cmax values were approximately two-fold greater than those in demographically-matched healthy volunteers. As there are no clinical trial data to establish a safe and effective dosing regimen for hepatically impaired patients, entacapone should be not be administered to patients with hepatic impairment (see **CONTRAINDICATIONS**).

Renal Impairment

The pharmacokinetics of entacapone were not significantly changed in patients with moderate to severe renal impairment and there is no need for dose adjustment. AURO-ENTACAPONE should be administered with caution to patients with severe renal disease (see PHARMACOKINETICS AND METABOLISM OF ENTACAPONE). There is no experience with entacapone in patients receiving dialysis.

Pregnant Women

There are no studies or clinical experience of the use of entacapone in pregnant women. Use of AURO-ENTACAPONE in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child (see TOXICOLOGY, Reproductive Studies).

Nursing Mothers

Studies in rats have shown that entacapone is excreted in milk.

It is not known whether entacapone is excreted in human milk. Since the safety of entacapone in infants is unknown, women should not breast-feed during treatment with AURO-ENTACAPONE.

Pediatrics

The safety and efficacy of entacapone in pediatric patients has not been established and use in patients below the age of 18 is not recommended.

Geriatrics

No adjustment of AURO-ENTACAPONE dosage is necessary in elderly patients.

Concurrent Diseases

AURO-ENTACAPONE and levodopa should not be given to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, pulmonary (including bronchial asthma), hepatic or renal disease (see CONTRAINDICATIONS).

AURO-ENTACAPONE should be administered with caution to patients with ischemic heart disease, biliary obstruction, or history of peptic ulcer disease or convulsions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies have been conducted in the mouse at dosages up to 600 mg/kg/day and in the rat at dosages up to 400 mg/kg/day. In the rat, the only drug-related finding was an increased incidence of renal tubular adenomas and carcinomas noted in males at doses of 400 mg/kg/day. 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 (8 x 200 mg = 1600 mg). In the mouse study, there was a high incidence of premature mortality in animals receiving the highest dose of entacapone (600 mg/kg/day, corresponding to 2 times the maximum recommended human dose on a mg/m^2 basis). Thus, the mouse study does not allow adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone in combination with levodopa/DDC has not been studied.

Mutagenesis

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 Sinemet, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

Teratogenicity

Reproduction studies have been performed in rats and rabbits at doses up to 1000 mg/kg/day and 300 mg/kg/day, respectively, of entacapone. Increased incidence of fetal variations was evident in litters from rats treated at the highest dose in the absence of overt maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximal recommended dose of 8 x 200 mg (1600 mg/day). Increased frequencies of abortion and late/total resorptions and decreased fetal weights were observed in litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUC 0.4 times those in humans receiving the maximal recommended daily dose) 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 litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in humans receiving the maximal recommended daily dose) or greater, in the absence of maternal toxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the maximal recommended daily dose) to female rats during the later part of gestation and throughout lactation produced no evidence of developmental impairments in the offspring.

Entacapone is always given concomitantly with levodopa/DDC inhibitor, which is known to cause visceral and skeletal malformations in rabbits. Although the teratogenicity of entacapone was assessed in animals, the teratogenic potential of entacapone in combination with levodopa/carbidopa was not assessed.

Impairment of fertility

No effect on fertility was observed in male and female rats treated with up to 700 mg/kg/day of entacapone (exposure achieved approximately 28 times higher than that in man after the maximum recommended daily dose of 8 x 200 mg/day).

Information for Patients

The following information should be discussed by physicians with patients and their caregivers:

1. Sudden Onset of Sleep

Physicians should alert patients that cases of sudden onset of sleep have been reported with entacapone in combination with levodopa/DDC inhibitor and/or other dopaminergic agents, and inform them that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with AURO-ENTACAPONE used in combination with levodopa/DDC inhibitor, such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking AURO-ENTACAPONE in combination with levodopa/DDC inhibitor. Patients should be advised to refrain from driving or

operating machines and to immediately contact their physician if they experience drowsiness or sudden onset of sleep.

2. Monitoring for melanomas

Patients should be advised that studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. Therefore, patients and healthcare providers are advised to perform periodic skin examinations when using AURO-ENTACAPONE.

3. Monitoring for prostate cancer

Patients should be informed that in a study of patients with early stage Parkinson's disease, who were treated with levodopa/carbidopa or entacapone in combination with levodopa/carbidopa for an average of about 3 years, prostate cancer was reported more frequently in the group of patients that received entacapone. It is not known if treatment with entacapone affects the risk of having prostate cancer. Therefore, physicians should emphasize to patients the importance of adhering to routine examinations for prostate cancer during extended treatment with entacapone.

4. Prolonged or persistent diarrhea

Patients should be informed that diarrhea may occur with entacapone and may have a delayed onset. Sometimes prolonged diarrhea has been associated with colitis (inflammation of the large intestine). Should transient, mild diarrhea occur, the patient should drink fluids and monitor for weight loss. If diarrhea persists, without any known cause, patient evaluation by a physician is recommended. If prolonged/persistent diarrhea is suspected to be related to AURO-ENTACAPONE, the drug should be discontinued. In case the prolonged diarrhea is due to AURO-ENTACAPONE, it seems to resolve usually within few days after stopping the drug. If the cause of prolonged diarrhea remains unclear or continues after stopping entacapone, then further diagnostic investigations should be considered.

5. Compulsive behaviors

Patients should be advised that intense urges to gamble, increased sexual urges, other intense urges such as excessive eating or spending, and the inability to control these urges have been reported while taking one or more of the medications that increase central dopaminergic tone, which are generally used for the treatment of Parkinson's disease, including AURO-ENTACAPONE. Prescribers should ask patients about the development of new or increased urges or cravings and should advise patients to report such new urges while being treated with AURO-ENTACAPONE. Because these urges have been reported to stop in some cases after dose reduction or stopping medication, physicians should consider these adjustments if a patient develops such urges while taking AURO-ENTACAPONE.

Drug Interactions

Protein binding

Entacapone is highly protein bound (98%). *In vitro* studies have shown that entacapone, at therapeutic concentrations, does not displace drugs of which a large proportion is bound to plasma proteins (e.g. warfarin, salicylic acid, phenylbutazone and diazepam). Entacapone is not markedly displaced by any of these drugs at therapeutic concentrations (see ACTIONS AND CLINICAL PHARMACOLOGY).

Drugs metabolized by Cytochrome P450

Data from in vitro studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 μM).

Other P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) were inhibited only by very high concentrations of entacapone (IC50 from 200 to greater than 1000 μM). The highest concentration of entacapone achieved with an oral 200 mg dose is approximately 5 μM and is not expected to inhibit these enzymes.

Drugs metabolized by Cytochrome P450 (CYP2C9)

Entacapone has been shown to inhibit the activity of cytochrome P450 2C9 in vitro and may potentially interfere with drugs whose metabolism is dependent on this isoenzyme, such as S-warfarin . However, in an interaction study in healthy volunteers, entacapone did not change the plasma levels of S-warfarin, while the AUC for R-warfarin increased on average by 18% [CI90 11-26%]. The INR values increased on average by 13% [CI90 6-19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

Drugs metabolized by the Catechol-O-methyltransferase (COMT):

The experience of the clinical use of entacapone with medicinal products that are metabolized by COMT (e.g. catechol-structured compounds: rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine, and paroxetine) is still limited (see **WARNINGS**). Regardless of their route of administration, including inhalation, drugs known to be metabolized by COMT should be used with caution in patients treated concomitantly with entacapone, as their interaction may result in increased heart rates, possible arrhythmias and excessive changes in blood pressure (see **WARNINGS**).

Non-selective MAO inhibitors: AURO-ENTACAPONE should not be given concomitantly with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of selective MAO-A and selective MAO-B inhibitors is equivalent to non-selective MAO-inhibition, therefore, they should not both be given concomitantly with AURO-ENTACAPONE and levodopa preparations. Non-selective MAO inhibitors must be discontinued at least two weeks prior to initiating therapy with entacapone (See **CONTRAINDICATIONS).**

Selegiline

In two multiple-dose interaction studies in patients with Parkinson's disease, no interactions between entacapone and selegiline (10 mg) were observed in the presence of coadministered levodopa/DDC inhibitor. More than 400 parkinsonian patients in phase 2 and 3 studies used selegiline in combination with entacapone and levodopa/DDC inhibitor without any apparent interactions (also see CONTRAINDICATIONS).

Tricyclic antidepressants and noradrenaline re-uptake inhibitors

In a single-dose study in healthy volunteers, no interactions between entacapone and imipramine were observed in the absence of coadministration of levodopa/DDC inhibitor.

The potential for interactions between entacapone and tricyclic antidepressants or noradrenaline re-uptake inhibitors has not been systematically evaluated in patients with Parkinson's disease. The experience on the clinical use of entacapone with tricyclic antidepressants and noradrenaline reuptake inhibitors (desipramine, maprotiline and venlafaxine) is limited. Therefore, patients should be carefully monitored when AURO-ENTACAPONE is administered in combination with these drugs.

Dopa Decarboxylase Inhibitors

Carbidopa

No interaction of entacapone with carbidopa were observed with the recommended dosage regimen; however, high single doses (in excess of 400 mg of entacapone) may decrease the bioavailability of carbidopa.

Benserazide

Pharmacokinetic interaction studies with benserazide have not been conducted.

Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5-10% more than from standard levodopa/carbidopa preparations. Consequently, undesirable dopaminergic effects may be more frequent when entacapone is added to levodopa/benserazide treatment. A larger reduction of the levodopa dose may be required when AURO-ENTACAPONE treatment is initiated in patients receiving levodopa/benserazide (see DOSAGE and ADMINISTRATION)

Drugs interfering with biliary excretion

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 AURO-ENTACAPONE. These include probenicid, cholestyramine, and some antibiotics (e.g. erythromycin, rifampicin, ampicillin and chloramphenicol).

Iron

Similar to levodopa, entacapone may impair the absorption of iron from the gastrointestinal tract. Therefore, AURO-ENTACAPONE and iron-containing supplements or multivitamins should be ingested at least 2 to 3 hours apart.

Hormone levels

Levodopa is known to depress prolactin secretion and increase growth hormone levels. Treatment with entacapone coadministered with levodopa/DDC inhibitor does not change these effects.

Laboratory Tests

Entacapone is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreased serum iron concentrations was noted in a clinical trial. 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 the rates of anemia or decreased hemoglobin levels.

The laboratory tests required during extended levodopa therapy should be normally conducted also during AURO-ENTACAPONE treatment.

ADVERSE REACTIONS

A total of 1450 patients with Parkinson's Disease received entacapone during the pre-marketing clinical trials. 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 for entacapone vs placebo 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%).

Incidence of Adverse Events in Placebo Controlled Trials

The most frequently observed adverse events reported with entacapone were dyskinesias/hyperkinesia (25%/10%), nausea (14%), abnormal urine (intensification of the color of urine, 10%), diarrhea (10%), dizziness (8%) and abdominal pain (8%). Dyskinesia, nausea and abdominal pain, may be more common with higher doses (> 1,400 mg/day) than with lower doses of entacapone.

Adverse events related to the treatment with entacapone are usually mild to moderate in severity, leading only rarely to discontinuation of the treatment.

Table 3: Adverse events, irrespective of causal relationship to study drug, occurring in ≥ 1% of Entacapone patients and > placebo during controlled Phase 3 studies.

Adverse Events by body system	Entacapone N=603 % of patients	Placebo N=400 % of patients
Autonomic Nervous System Disorders		
Hypotension postural	4.3	4.0
Body As A Whole - General Disorders		
Fatigue	6.1	3.5
Pain	6.0	4.5
Back pain	5.0	3.0
Sweating increased	3.6	3.0
Asthenia	1.8	1.3
Weight decrease	1.7	0.5
Fever	1.3	0.5
Syncope	1.0	0.8
Central & Peripheral Nervous System Disorders		
Dyskinesia	25.2	14.8
Hyperkinesia	9.5	5.0
Hypokinesia	8.6	7.5
Dizziness	7.5	6.0
Ataxia	1.2	0.5
Speech disorder	1.2	0.8
Gastrointestinal System Disorders		
Nausea	13.8	7.5
Diarrhea	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
Dyspepsia	2.3	0.8
Flatulence	1.5	0.3
Anorexia	1.5	1.3
Gastrointestinal disorders	1.0	0.3
Gastritis	1.0	0.3
Musculoskeletal System Disorders		

Adverse Events by body system	Entacapone N=603 % of patients	Placebo N=400 % of patients
Arthralgia	1.8	1.5
Platelet, Bleeding & Clotting Disorders		
Purpura	1.5	0.8
Psychiatric Disorders		
Hallucinations	4.1	4.0
Nightmares	2.2	1.8
Anxiety	2.0	1.3
Agitation	1.7	0.3
Confusion	1.7	1.5
Somnolence	1.7	0.3
Amnesia	1.3	0.8
Sleep disorder	1.3	0.8
Reproductive Disorders, Male		
Prostatic disorder	1.0	0.3
Resistance Mechanism Disorders		
Infection bacterial	1.3	0.0
Respiratory System Disorders		
Dyspnoea	2.7	1.3
Bronchitis	1.2	1.0
Secondary Terms - Events		
Fall	4.1	3.5
Skin And Appendages Disorders		
Rash	3.6	3.0
Special Senses Other, Disorders		
Taste perversion	1.0	0.3
Urinary System Disorders		
Urine abnormal	9.5	0.0
Cystitis	1.2	0.5

Additional adverse events that are not included in the above table but that have been identified as common adverse events associated with the use of entacapone in clinical trials and post-market spontaneous reports include insomnia, parkinsonism aggravated, and dystonia.

Adverse Events reported in <1% of patients treated with entacapone in Phase 3 trials

Body As A Whole - General Disorders: malaise, hot flushes, temperature changed sensation, aspiration, oedema generalised, carpal tunnel syndrome, leg pain;
Cardiovascular Disorders, General: hypertension, heart valve disorders;
Central & Peripheral Nervous System Disorders: hypoaesthesia, muscle contractions involuntary, eye abnormality, hypotonia; impulse control disorders (obsessive-compulsive disorder, hypersexuality, akathisia, compulsive lip biting, gambling, libido increased, obsessive thoughts, pathological gambling, sexual activity increased);
Endocrine Disorders: hyperthyroidism;
Gastrointestinal System Disorders: gastroenteritis, oesophagitis, tooth disorder, saliva increased, dysphagia, faeces discoloured, diverticulitis, change in bowel habits, faecal abnormality;
Heart Rate And Rhythm Disorders: extrasystoles, bradycardia, bundle branch block, fibrillation atrial;
Liver & Biliary System Disorders: gamma-gt increased, cholelithiasis, bilirubinaemia, cholangitis;
Metabolic & Nutritional Disorders: hyperglycaemia, hypoglycaemia, phosphatase alkaline increased, hypercholesterolaemia;
Musculoskeletal System Disorders: bursitis, arthritis, tendinitis;
Myo-, Endo-, Pericardial & Valve Disorders: angina pectoris; ***Platelet, Bleeding & Clotting Disorders:*** epistaxis, thrombocytopenia;
Psychiatric Disorders: nervousness, thinking abnormal, concentration impaired, dreaming abnormal, delusion, paranoid reaction;
Reproductive Disorders, Female: breast fibroadenosis;
Reproductive Disorders, Male: impotence, sexual function abnormal;
Resistance Mechanism Disorders: herpes simplex;
Respiratory System Disorders: pneumonia, pharyngitis, sinusitis;
Secondary Terms - Events: inflicted injury;
Skin And Appendages Disorders: pruritus, skin disorder, dermatitis, eczema, dermatitis fungal;
Special Senses Other, Disorders: taste loss;
Urinary System Disorders: urinary incontinence, haematuria, albuminuria, dysuria, nocturia, renal pain;
Vascular (Extracardiac) Disorders: skin cold clammy, claudication intermittent;
Vision Disorders: diplopia, conjunctivitis, cataract, photopsia;
White Cell & Res Disorders: leucopenia.

The following adverse events were reported only once but are considered clinically important: hepatic function abnormal, hepatic enzymes increased (> 3 times ULN), cholecystitis, allergic reaction, and dopamine dysregulation syndrome.

Myocardial Infarction and Other Ischemic Heart Disease Events

Myocardial infarction and other ischemic heart disease events have been reported with the use of entacapone in combination with levodopa/carbidopa in clinical trials.

In 13 controlled, double-blind studies, 2082 patients (median age of approximately 65) with end-of-dose motor fluctuations ("wearing-off") were treated with entacapone in combination with levodopa/DDC inhibitor and 1582 patients (median age of approximately 65) received levodopa/DDC inhibitor for an average duration of approximately 6 months. The incidence rate of myocardial infarction was 0.53% and 0.32% for entacapone[†] and levodopa/DDC inhibitor, respectively. Other ischemic heart disease adverse events were reported in 1.54% of patients treated with entacapone and 0.82% of patients treated with levodopa/DDC inhibitor.

A study was conducted in which patients with early Parkinson's disease (median age of 61) initiated levodopa treatment with either levodopa/carbidopa/entacapone or levodopa/carbidopa. The average treatment duration was approximately 3 years. Myocardial infarction was reported in 1.9% of patients treated with levodopa/carbidopa/entacapone compared to 0% of patients treated with levodopa/carbidopa. Other ischemic heart disease adverse events were reported in 1.9% of patients treated with entacapone and in 3.5% of patients who received levodopa/carbidopa. AURO-ENTACAPONE is not indicated for the treatment of early Parkinson's disease.

Entacapone therapy should be administered with caution to patients with ischemic heart disease or risk factors for cardiovascular disease. Periodic evaluation of cardiovascular function is recommended during extended therapy with entacapone.

Prostate Cancer Adverse Events

Prostate cancer has been reported elderly males during the use of entacapone in combination with levodopa/carbidopa in clinical trials (see PRECAUTIONS-Prostate Cancer).

In the study of patients with early Parkinson's disease who initiated levodopa treatment with either levodopa/carbidopa in combination with entacapone or levodopa/carbidopa (median age of 61), and remained on treatment for an average duration of approximately 3 years, prostate cancer was reported in 3.7% of males treated with levodopa/carbidopa in combination with entacapone and in 0.9% of males treated with levodopa/carbidopa. There was a numerical increase in the probability of developing prostate cancer with increased duration of treatment, but this was not statistically significant. AURO-ENTACAPONE is not indicated for the treatment of early Parkinson's disease.

In 13 controlled, double-blind studies that included patients with end-of-dose motor fluctuations (median age of approximately 65), in which the average treatment duration was approximately 6 months, prostate cancer was reported at similar frequencies in males treated with entacapone (0.31%) and in males treated with levodopa/DDC inhibitor (0.20%).

[†] Entacapone refers to entacapone in combination with levodopa/DDC inhibitor

The clinical relevance of these observations is not known. Physicians are advised to emphasize to patients the importance of adhering to regular examinations for prostate cancer during extended treatment with entacapone (see PRECAUTIONS-Information for Patients).

Laboratory Findings

Slight decreases in hemoglobin, erythrocyte count and hematocrit have been reported during entacapone treatment. The underlying mechanism may involve decreased absorption of iron from the gastrointestinal tract. During long-term treatment (6 months) with entacapone a clinically significant decrease in haemoglobin has been observed in 1.5% of patients.

Post-Introduction Reports

Voluntary reports of adverse events that have been received since market introduction that are not listed above, are listed in Table 4. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 4: Entacapone Post-Market Spontaneous Adverse Event Reports.

Adverse Event	Frequency			
	Common (≥1%)	**Uncommon (<1% and ≥0.1%)**	**Rare (<0.1% and ≥0.01%)**	**Very rare (<0.01%)**
Liver and Biliary System Disorders				
Hepatitis with mainly cholestatic features				X
Clinically significant increases in liver enzymes			X	
Central and Peripheral Nervous System Disorders				
Neuroleptic Malignant Syndrome				X
Gastrointestinal disorders				
Colitis				X
Musculoskeletal System Disorders				
Rhabdomyolysis				X
Skin and Appendage Disorders				
Erythematous/maculopapular rash			X	
Urticaria				X
Skin, hair, beard and nail discolorations				X

Isolated cases of hepatic failure and severe, serious skin reactions resembling erythema multiforme and toxic epidermal necrolysis have been reported in patients treated with entacapone.

Isolated cases of angioedema have been reported after initiation of treatment with levodopa/DDC inhibitor/entacapone.

Patients treated with entacapone in combination with levodopa/DDC inhibitor have very rarely reported falling asleep while engaged in activities of daily living, including operation of motor vehicles, which has sometimes resulted in accidents (See WARNINGS).

Pathological (compulsive) gambling has been reported in post-market data, including those in the literature, for antiparkinson drugs. Impulse control disorders: pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, binge eating/compulsive eating have been reported in patients treated with dopamine agonists and/or other dopaminergic treatments such as entacapone in association with levodopa; these were reported at a rate of 0.04 per 1000 patient years. Safety data from various sources including literature, clinical trials, and post-market analysis have described an addictive pattern of dopamine replacement therapy, in which patients use doses in excess of those required to control their motor symptoms (dopamine dysregulation syndrome), and was reported at a rate of 0.002 per 1000 patient years. These behavioral symptoms were generally reversible upon dose reduction or treatment discontinuation (see PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms

The COMT inhibition by AURO-ENTACAPONE (entacapone) is dose-dependent; a massive overdose of AURO-ENTACAPONE may, therefore, produce a 100 % inhibition of COMT enzyme in man, and thereby prevent the metabolism of endogenous and exogenous catechols. The post-marketing data includes isolated cases of overdose in which the reported highest daily dose of levodopa and entacapone has been at least 10,000 mg and 40,000 mg, respectively. The acute symptoms and signs in these cases of overdose included agitation, dsyskinesia, confusional state, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration mydriasis, decreased activity, somnolence, hypotonia, discolouration of the skin, tongue and conjunctiva, chromaturia, mild renal failure, neuroleptic malignanat syndrome and urticaria.

Management of overdose: Hospitalization is advised and general supportive care is indicated. Management is symptomatic; there is no known antidote to entacapone. The drug is rapidly absorbed and eliminated with a short mean residence time. There is no experience with dialysis or hemoperfusion, and these procedures are unlikely to be of benefit, because entacapone is highly bound to plasma proteins. An immediate gastric lavage and repeated doses of charcoal over time may hasten the elimination of AURO-ENTACAPONE by decreasing the absorption/reabsorption of AURO-ENTACAPONE from GI tract. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. In managing overdosage, the possibility of interaction among drugs,

especially catechol-structured drugs, should be borne in mind. For up-to-date information on the management of a suspected drug overdose, contact a regional Poison Control Center.

DOSAGE AND ADMINISTRATION

Method of Administration

AURO-ENTACAPONE (entacapone) has no antiparkinsonian effect of its own and therefore should always be administered simultaneously with each levodopa/carbidopa or levodopa/benserazide dose. The efficacy of entacapone as an adjunct to controlled-release levodopa/DDC inhibitor preparations has not been established.

AURO-ENTACAPONE is taken orally with or without food. (See ACTION AND CLINICAL PHARMACOLOGY).

Dosage

The recommended dose of AURO-ENTACAPONE is one 200 mg tablet administered concomitantly with each levodopa/carbidopa or levodopa/benserazide dose up to 8 times daily (1600 mg/day).

Because entacapone enhances the bioavailability and therefore the central effects of levodopa, it may be necessary to adjust the dosage of levodopa during the initial days to weeks of entacapone therapy in order to reduce levodopa-related dopaminergic adverse reactions, e.g., dyskinesias, nausea, vomiting and hallucinations. In some cases, it may be necessary to reduce the daily dosages of levodopa by about 10-30%. This can be achieved through either reducing the dose of the levodopa preparation itself, or by extending the interval between doses, according to the clinical condition of the patient.

In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa had been greater than or equal to 800 mg, or if patients had moderate or severe dyskinesias before beginning treatment. The average reduction in daily levodopa dose for patients in clinical trials requiring levodopa dose reduction was about 25% (more than 58% of patients with levodopa doses above 800 mg daily required such a reduction).

Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations slightly (5-10%) more than from standard levodopa/carbidopa preparations. Therefore, patients who are taking standard levodopa/benserazide preparations may need a larger reduction of levodopa dose when entacapone is initiated.

Patients with Impaired Hepatic Function

As there is no clinical trial data to establish a safe and effective dosing regimen for hepatically impaired patients, entacapone should be not be administered to patients with hepatic impairment (see **CONTRAINDICATIONS*)***

Patients with Impaired Renal Function

No dose adjustment of AURO-ENTACAPONE is necessary in patients with moderate to severe renal impairment. There is no experience with entacapone in patients receiving dialysis therapy.

Elderly

No dose adjustment is required in elderly patients.

Discontinuation of AURO-ENTACAPONE

Rapid withdrawal or abrupt reduction in the AURO-ENTACAPONE dose could lead to emergence of signs and symptoms of Parkinson's disease (see Clinical Pharmacology, Clinical Trials) and may lead to a symptom complex resembling neuroleptic malignant syndrome (see **PRECAUTIONS**, **Neuroleptic Malignant Syndrome**). This syndrome should be considered in the differential diagnosis for any patient who develops high fever or severe rigidity. If a decision is made to discontinue treatment with AURO-ENTACAPONE, patients should be monitored closely and other dopaminergic treatments should be adjusted as needed. Although tapering entacapone has not been systematically evaluated, it seems prudent to withdraw patients slowly if the decision to discontinue treatment is made.

PHARMACEUTICAL INFORMATION

Drug Substance

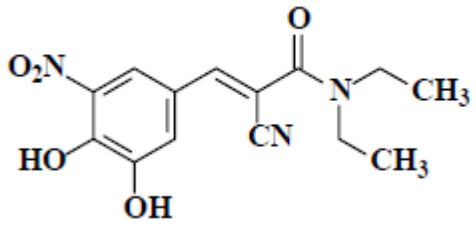
Proper Name: entacapone

Chemical Name: *(2E)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N.N-diethylprop-2-enamide*

Empirical Formula: $C_{14}H_{15}N_3O_5$

Molecular Weight: 305.29 g/mol

Structural Formula:



Description: Greenish-yellow or yellow powder

Solubilty: Practically in soluble in water

Log P : 2.8

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form	**Tablets**
Strength	**200 mg**
Description	Brownish-Orange coloured , film-coated, oval shaped tablets debossed "Y 17" on one side and plain on the other side.
Composition	**Non-medicinal Ingredients:** Lactose monohydrate, Cellulose Microcrystalline, Mannitol, Sodium starch glycolate, croscarmellose sodium, Hydrogenated vegetable oil and magnesium stearate **Coating Ingredients:** Opadry Orange 06F530001: It contains hypromellose, titanium dioxide, macrogol , iron oxide yellow & iron oxide red.
Packaging	Blister Pack of 4 x 7's tablets. HDPE Packs of 10 , 100 & 200 tablets.

Storage

Store at room temperature (15° and 30°C).

PHARMACOLOGY

ANIMAL PHARMACOLOGY

In Vitro

Entacapone is a potent inhibitor of COMT *in vitro* suppressing COMT activity in crude tissue preparations (brain, duodenum, rat and human red blood cells, liver) with IC50-values ranging from 0.01 μM for rat brain S-COMT to 0.16 μM for rat liver S-COMT. The IC50-values for (*Z*)-OR-611, the (*Z*)-isomer of entacapone, were of approximately the same magnitude as those measured for entacapone. The IC50-values for human and rat RBC were similar.

The K_i-value, which indicates the affinity of the inhibitor to the enzyme, was 14 nM for rat liver sol-COMT. The enzyme kinetic studies revealed that entacapone is a reversible and selective inhibitor of the COMT-enzyme.

Ex Vivo

In *ex vivo* tests, following oral or i.v. administration of entacapone 10 mg/kg, S-COMT was inhibited generally in good correlation with *in vitro* IC50-values of the same tissue, excepting the brain which reflects poor penetration of entacapone into the CNS.

In most tissues, inhibition of COMT was transient indicating that entacapone is a reversible COMT-inhibitor. In rats, the inhibition of duodenal COMT activity was more complete and sustained as compared to other tissues.

In Vivo

Levodopa Pharmacokinetics

Entacapone administered orally at doses of 0.3 - 30 mg/kg, caused a dose-dependent and sustained inhibition of 3-OMD formation from levodopa in rat serum. The inhibition of 3-OMD formation was reflected by elevated levodopa concentrations in serum. Accordingly, addition of entacapone (30 mg/kg) to levodopa/ carbidopa treatment prolonged the elimination half-life of levodopa about 5-fold after *i.v.* levodopa and about 2-fold after oral levodopa.

Peripheral COMT Inhibition and Central Levodopa Metabolism

Entacapone added to the levodopa/carbidopa treatment reduced rat striatal 3-OMD levels and increased both dopamine and levodopa concentrations. Striatal HVA levels were not reduced, supporting the inhibition of peripheral COMT activity by entacapone. Following addition of entacapone to levodopa/carbidopa treatment, the dose of levodopa could be decreased by 70 % and reach the same striatal dopamine concentration as with levodopa/carbidopa alone. A significant reduction in 3-OMD concentration and a significant increase in levodopa concentration was observed with entacapone treatment, indicating that entacapone improved the availability of levodopa in the brain.

Efficacy of entacapone in animal models of Parkinson's disease

Entacapone significantly improves and sustains the dopaminergic effect of levodopa therapy, when given in combination with carbidopa, in various animal models of Parkinson's disease.

The locomotor activity of hypokinetic reserpine treated mice was potentiated by the oral administration of entacapone at doses of 3, 10 and 30 mg/kg to the levodopa/carbidopa treatment.

In rats with unilateral 6-hydroxy-dopamine (6-OHDA) induced lesions of the substantia nigra, entacapone administered orally at doses of 1, 3 and 10 mg/kg potentiated levodopa/carbidopa induced contralateral circling behavior up to approximately 3 hours post-dosing. In another study, the addition of entacapone, administered orally at dose of 10 mg/kg, to the levodopa/carbidopa treatment allowed a 50% reduction in the levodopa dose without reducing the contralateral turning.

Entacapone, at oral doses of 12.5 mg/kg, significantly increased and potentiated the antiparkinsonian effect of low dose levodopa/carbidopa in MPTP treated marmosets.

Special studies

Three short-term studies (8 to 15 days) were conducted in rats to compare the toxicity of entacapone and another COMT-inhibitor (tolcapone) at doses ranging from 200 to 600 mg/kg/day. All of these studies examined potential hepatotoxic effects of these two compounds and one was designed to investigate the association of toxicity with uncoupling of oxidative phosphorylation *in vivo*. Signs of hepatotoxicity (centrilobular hypertrophy, necrosis, vacuolation) were observed in rats treated with tolcapone at doses which caused mortality (400 mg/kg) (plasma exposure at 500 mg/kg/day corresponds to 26 times that in humans at the maximum recommended daily dose of 600 mg); 300 mg/kg may be a threshold dose since 1 of 19 animals exhibited hepatic changes similar to those found at the higher doses. Increased body temperature and changes in mitochondrial respiration and ATP/ADP ratios were found in animals treated with tolcapone ($\geq$300 mg/kg) and dinitrophenol, a known uncoupler of oxidative phosphorylation. In contrast, neither hepatotoxic effects (histopathological) nor effects on oxidative phosphorylation were observed with entacapone at any of the doses tested (plasma exposure at the highest dose of 600 mg/kg/day corresponds to 26 times that in humans receiving the maximum recommended daily dose of 1600 mg). The relevance of these findings to man is unknown.

Treatment	Dose mg/kg	Mortality	Liver microscopic findings	Body Temp	Mitochondrial ATP/ADP (liver)	Respiratory control ratio	AUC 0-24h hμ·g/mL
Entacapone	200	0	none (n=6)				159 (10x human)
	300	0	none (n=20)	-	-	-	
	400	0	none (n=5)	-			
	500	0	none (n=20)	-	-	-	
	600	0	none (n=11)	-			415 (26x human)
Tolcapone	200	0	none (n=6)				325 (4x human)
	300	0	Centrilobular hypertrophy, vacuolation (1/19 animals)	↑	↓ (marginal)	↓	
	400	↑	Centrilobular hypertrophy, necrosis, vacuolation (5/5 animals)	↑			
	500	↑	Centrilobular hypertrophy, vacuolation (14/20 animals)	↑	↓	↓	
	600	↑	Centrilobular hypertrophy, focal necrosis, vacuolation (9/11 animals)	↑			
Dinitro-phenol	20	0	Centrilobular hypertrophy, necrosis (3/12 animals)	↑	↓	↓	
Blank = not evaluated; - = no different from control; ↑= increase; ↓= decrease							

In an *in vitro* study in rat liver mitochondria, entacapone had no influence on membrane potential at concentrations less than 100 μM, while the other COMT inhibitor (tolcapone) and 2, 4-dinitrophenol caused a concentration-dependent decrease in mitochondrial membrane potential. The results of this study indicate that entacapone does not uncouple oxidative phosphorylation since it had no effect on membrane potential at reasonable concentrations.

Concentration required for 50% decrease in mitochondrial membrane potential *in vitro*

Entacapone	Tolcapone	Dinitrophenol
>100 μM	3-5 μM	2 μM

TOXICOLOGY

Acute Toxicity

Species	Sex	Dose (mg/kg)	Route	LD50 (mg/kg)
Mouse	5 M	1000, 1500, 2000	oral	2000
Mouse	5 F	2000	oral	2000
Mouse	10 F	1000, 1500, 2000, 2500	oral	>2500
Mouse	5 M	1000, 1500, 2000	oral	>1900 (z-isomer)
	5 F	1500		>1900 (z-isomer)
Rat	5 F	1500, 1750, 2000	oral oral	>2000
Rat	5 M	2000		
Rat	5 M	1000/1000/250-1500/1500/375 (Levodopa/benserazide: 2000/500)		Entacapone/levodopa/ benserazide:1400/1400/350 Levodopa/benserazide:LD_{50}> 2000/500

The acute toxicity of the *(Z)*-isomer is similar to that of (*E*)-isomer of entacapone and are considered to be low.

Subchronic/Chronic Toxicity with Entacapone

Species Strain	Dosage (mk/kg/day orally)	N/Dose	Duration	Findings
Rat Han: Wistar	0, 15, **95***, 600 by gavage in MC	10 F/10 M	28 days	Mortality: 5 deaths during the study but none were treatment related. 600 mg/kg/d: ↓ body weight gain and food consumption in M; ↑ body weight-related liver weight in F. Treatment rats passed coloured urine. ↓ levels of hemoglobin, erythrocytes, hematocrit, serum albumin and urea and ↑ levels of ALAT. Dose-dependent ↓ in ASAT and lactate dehydrogenase . Urine analysis: ↑ erythrocytes, chloride and sodium. Macroscopic & Microscopic examinations: Fur and tail discolouration mainly. 95 & 600 mg/kg: Dose-related incidence of pre-and post-dose salivation . Microscopic pathology did not reveal any treatment-related changes.
Dog Beagle	0, 10, **80***, (600)-200 by gavage in MC	3 F/3 M	28 days	10 mg/kg/d: 1F vomited on one day. 80 mg/kg/d: Occasional vomiting in some animals and a slight initial in ↓ food consumption. The animals also tended to pass coloured urine and feces. 600 mg/kg/d: Marked clinical signs over the first 3 days. Animals vomited often and were subdued, and body weight ↓ markedly. Dose level ↓ to 400 mg/kg/d from day 4. Animals salivated, had orange/red urine and dark feces, but the incidence of vomiting was ↓. Because the body weight still ↓, the animals were not dosed in week 3. During that week there were no clinical signs and the body weight gain was normal. When treatment was restarted in week 4 at 200 mg/kg/d, the animals passed coloured urine and feces and two of them vomited on one occasion each. No treatment-related abnormal findings were observed in ophthalmoscopy, hematology, clinical chemistry, urine analysis (except the colour) and in macroscopic and microscopic pathology.
Rat (Crl:CD^{R}) SpragueDawley	0, 10, **65***, 400 by gavage in MC	12 F/12 M	13 weeks	Mortality: 4 animals died but no changes at autopsy were related to treatment. 400 mg/kg/d: rats had stained fur (yellowish); postdose salivation was regularly observed throughout the study; ↓ body weight gain in both sexes during the first half of the study. ↓ levels of hemoglobin, hematocrit, glucose and triglycerides. Lymphocyte count slightly ↑. 65 and 400 mg/kg/d: Dose-related coloured urine (yellow-orange) throughout the study. ↑ hemoglobin in urine. Macroscopic examination revealed fur and skin discolouration and abnormal coloured contents of caecum. Microscopic pathology did not reveal any treatment-related findings.

Species Strain	Dosage (mk/kg/day orally)	N/Dose	Duration	Findings
Dog Beagle	0, 10, **45***, (200) -300 in gelatine capsules	4 F/4 M	13 weeks	Mortality: No deaths. 300 mg/kg/d: coloured urine and dark feces. Fur of animals became stained as the study progressed. Pre- and post-dose salivation and occasional vomiting. Body weight gain of M and F of only 22% & 36% respectively. ↓ food consumption at beginning of study and after dose level ↑ to 300 mg/kg/d. Slightly ↑ specific gravity of urine. No treatment-related changes in ECG, blood pressure, hematology and clinical chemistry. Dose-related ↑ in relative liver weight in M & F. Macroscopic pathology did not reveal any treatment-related changes. The only histopathological finding noted was a marginal increase in cytoplasmic vacuolation in the centrilobular areas in the liver. It was noted in 1, 1 and 4 cases at dosages of 10, 45 & 300 mg/kg/d, respectively. The significance of this finding is equivocal. 45 mg/kg/d: coloured urine and dark feces were observed. 10 mg/kg/day: dark feces were observed occasionally.
Rat (Crl:CD^{R}) SpragueDawley	0, 20, **90***, 400 by gavage in MC	20 F/20 M	52 weeks	Mortality: 18 animals died or were killed, none of these were treatment related. All doses: dose-related coloured urine (yellow-orange) and postdose salivation. 90 & 400 mg/kg/d: dark feces, yellow staining of fur. 400 mg/kg/d: ↓ body weight gain, low hematocrit values and ↑ serum inorganic phosphorus (F): ↑ serum ALP, low thrombocyte count, ↑ serum sodium and potassium (M); ↑ water consumption; ↓ levels of hemoglobin and erythrocytes; ↓ ALAT, ASAT and urinary sodium and chloride concentrations; ↑ incidence of chronic myocarditis;
Dog Beagle	0, 20, **80***, 300 in gelatine capsules	4 F/4 M	52 weeks	Mortality: no deaths All doses: no treatment-related changes in ophthalmoscopy, ECG and blood pressure; no treatment-related histopathological changes observed. 20 mg/kg/d: dark feces and dark yellow urine occasionally observed. 80 & 300 mg/kg/d: dark feces, bright orange urine (degree of colouration dose related), yellow-orange staining of coat. 300 mg/kg/d: M & F: active resistance to dosing; ↓ body weight gain and food consumption; hypochromic microcytic anaemia characterised by low packed cell volume, Hb concentration, mean cell volume and mean cell Hb and slightly low erythrocyte count; transiently low plasma phospholipid, total cholesterol and plasma urea concentrations; absolute thyroid weights and body weight-relative thyroid and submandibular salivary gland weights slightly higher than in controls. F: Salivation; ↓ number of cells of the erythroid series in the bone marrow in 2 animals after 52 weeks.

* No Toxic Effects Level (NTEL). MC = 0.05 or 1.2 % methylcellulose

Combination toxicity with L-DOPA + Carbidopa

Species Strain	Dosage (mg/kg/day orally)	N/Sex	Duration	Findings
Rat (Crl:CD^{R}) Sprague Dawley	Entacapone 0, 10, 60, 600 L-DOPA/Carbidopa 50/50 by gavage in 1.2% Methylcellulose	10 F/10 M	28 days	Mortality: 6 premature deaths during the study; 4 deaths occurred at high-dose level, 1 death at intermediate-dose level and 1 death at control level. Five cases were confirmed to be due to gavage technique (perforation of esophagus). In 1 case at high-dose level the cause of death could not be confirmed, but it was possibly caused by gavage technique. However, in this case the treatment relationship cannot be excluded. Signs/pathology: There were no major deviations in clinical signs, hematology, clinical chemistry or urine analysis from the signs observed in the 28-day oral toxicity study with entacapone alone. Marginal ↓ in blood glucose. Macroscopic and microscopic examination of different organs and tissues did not reveal any treatment-related pathological changes.
Rat (Crl:CD^{R}) Sprague Dawley	Entacapone/L-DOPA/ Carbidopa: 0/ 0/ 0; 20/20/5; 50/ 50/ 12.5; 120/120/30; 120/0/0; 0/120/30 by gavage in 0.5% Methylcellulose	10 F/10 M	13 weeks	Mortality: 2 premature deaths which were considered unrelated to treatment. Signs/pathology: the combination of entacapone, levodopa and carbidopa for 13 weeks at the dose level of 120/120/30 mg/kg/d was associated with ↓ body weight gain, clinical signs induced by levodopa/carbidopa alone or entacapone alone and minor focal erosive lesions in stomach. The macroscopic examination revealed fur and gastric epithelium discolourations in entacapone-treated rats. In microscopic examination, minor local erosive lesions of the gastric mucosa were seen in 3/20 rats of the 120/120/30 mg/kg/day group, in 1/10 rats of the 0/120/30 mg/kg/d group and in 1/10 rats of the 20/20/5 mg/kg/d group.
Cynomolgus monkey	Entacapone/L- DOPA/Carbidopa: 0/ 0/ 0; 20/20/5; 40/40/10; 80/80/20; 80/0/0; 0/80/20 by gavage in 0.5% Methylcellulose	4 F/4 M	13 weeks	Mortality: there were no deaths. Signs/pathology: The combination of entacapone, levodopa and carbidopa for 13 weeks at the dose level of 80/80/20 mg/kg/d was associated with ↑ dopaminergic clinical signs (e.g. stereotypies, chorea, dystonia) which were comparable to those seen in monkeys without entacapone. Discoloured urine in groups receiving 40-80 mg/kg/d entacapone. Dark feces were noted in animals receiving the highest dose of entacapone. No treatment-related macroscopic or microscopic changes were observed.

No distinct organ toxicity was observed in chronic toxicity studies. Entacapone did not increase the toxic effects of L-DOPA + Carbidopa in combination toxicity studies.

Renal Toxicity

In a 1 year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600 mg) caused an increased incidence in male rats of nephrotoxicity 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.

Teratological and Reproductive Studies

In the Segment I study, entacapone did not have any effect on male or female fertility up to doses of 350 mg/kg twice daily. The exposure achieved in this study was approximately 50 times higher than the average exposure in man (AUC_{man} with 6 x 200 mg).

In the Segment II studies, entacapone was not teratogenic up to doses of 500 mg/kg twice daily (1000 mg/kg/day), which approximates 100 times higher than the average exposure in man. The rabbit did not tolerate entacapone as well as the rat, the dose increment being limited by maternal toxicity and only 5 times higher exposure was achieved than the average exposure in man. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUCs 0.4 times those in humans receiving the maximum recommended therapeutic dose of 1600 mg/day) or greater.

In the Segment III studies, maternal treatment with entacapone did not affect the pre- and post-natal development or the subsequent growth development or the fertility of the F1 generation. The exposure achieved in these studies was up to 50 times higher than the average exposure in man.

Mutagenicity Studies with Entacapone

STUDY	DOSE-RANGE of entacapone	RESULT	LOWEST POSITIVE DOSE
Bacterial mutagenicity (S.typh. TA98, TA100, TA1535, TA1537; E. coli WP2 pKM101, WP2 uvrA pKM101); ± S9	15.625 - 2000 µg/plate	Negative	
Mammalian cell mutagenicity (mouse lymphoma L5178Y (Tk+/) *in vitro*); ± S9	2.5 - 400 µg/ml	Positive	At constant concentration range of 25-50 µg/ml
DNA-binding *in vitro* (calf thymus DNA); - S9	20, 25 or 50 µg of ^{14}C-entacapone	Negative	
Chromosomal aberration in human lymphocytes *in vitro*; ± S9	5 - 400 µg/plate	Positive only with S-9 mix	Excluding gaps 400 µg/ml; Including gaps 100 µg/ml
Micronuclei *in vivo* in polychromatic erythrocytes in mice	40, 200 or 1000 mg/kg orally; 35 mg/kg *i.v.*	Negative	
Rat liver UDS *in vivo/in vitro*	600 or 2000 mg/kg, orally	Negative	

Entacapone was not mutagenic in the Ames bacterial mutagenicity tested in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* in the presence and absence of metabolic activation (S-9 mix). Entacapone induced a significant increase in TK mutant frequency in L5178Y mouse lymphoma cells at a concentration range of 25 - 150 µg/mL with or without S-9 mix. The scoring of the number of wells containing small and large colonies showed that the majority of entacapone induced mutants were of the small colony type which indicates a chromosome-type damage of entacapone. *In vitro*, no substantial amount of entacapone seems to bind to DNA when thymus DNA was exposed to 25 - 50 µg/mL of entacapone. Bacteria, which do not possess chromosomes, were not affected by entacapone. Hence, the negative DNA-binding data is in good correlation with the results of Ames test strengthening the hypothesis that the damage induced by entacapone is at the chromosomal level.

In *in vitro* chromosomal aberration test with human lymphocytes, entacapone induced increases in chromosomal aberrations only in the presence of S-9 mix. The significant increases in the frequency of aberrant metaphases were observed at 400 µg/mL (1.3 mM) of entacapone. When mitotic indices were scored, entacapone was more toxic to the cells in the absence of S-9 mix than in its presence, the concentration difference being approximately 5-fold. Observed differences in mitotic indices could be due to differences in the treatment period, i.e. continuous and pulse treatment without and with S-9-mix, respectively.

Entacapone did not induce chromosomal or any other damage which leads to micronucleus formation in polychromatic erythrocytes of treated mice 24, 48 or 72 h after oral administration of a single MTD dose of 1000 mg/kg, or 24 h after a single *i.v.* dose of 35 mg/kg.

Mutagenicity Studies of Entacapone in combination with L-DOPA + Carbidopa

STUDY	DOSE-RANGE OF ENTACAPONE	RESULT
Bacterial mutagenicity (S.typh. TA98, TA100, TA1535, TA1537); ± S9 E coli WP2 pKM101, WP2 uvrA pKM101); ± S9	50 - 5000 µg/plate	Negative Negative
Micronuclei *in vivo* in polychromatic erythrocytes in mice	40, 200 or 1000 mg/kg orally	Negative

*The ratio of 4:4:1 of entacapone: L-DOPA: carbidopa at each dose-level was employed in the bacterial mutagenicity tests. In the mice micronucleus test L-DOPA 40 mg/kg + carbidopa 10 mg/kg were administered orally, concomitantly with various doses of entacapone.

Combination treatment with L-DOPA + carbidopa + entacapone was not mutagenic in the Ames bacterial mutagenicity test, tested in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* in the presence and absence of metabolic activation (S-9 mix). The highest dose-level of entacapone was shown to be toxic to the test bacteria.

In mice, entacapone (up to 1000 mg/kg *p.o.*) did not induce micronuclei in polychromatic erythrocytes when administered concomitantly with L-dopa + carbidopa (40 + 10 mg/kg *p.o.*)

Carcinogenicity Studies

Duration,Species,N	Dosage (mg/kg/d orally) by gavage in MC#	N of animals died M/F	Survival % corresponding to dosage	Exposure factor * relative to human dosing 200 mg , 6 times a day	Findings during the course of study and at necropsy
104 weeks, Mouse Crl:CD-1 50 F/50 M	0, 0, 20, 100, 600	22M + 33F 26M + 31F 23M + 29F 23M + 33F 36M+ 41F**	M: 56 ;F: 34 M: 48 ;F: 38 M: 54 ;F: 42 M: 54 ;F: 34 M:28 ; F -	 M: 0.4 ;F: 0.8 M: 24 ;F: 32	- - - - Food consumption decreased slightly (F)
104 weeks, Rat Crl:CD^{R} (Sprague Dawley) 50 F /50 M;	0, 0, 20, 90, 400	34M + 31F 26M + 27F 32M + 32F 32M + 31F 33M + 36F	M: 32 ;F: 38 M: 48 ;F: 46 M: 36 ;F: 36 M: 36 ;F: 38 M: 34 ;F: 28	 M: 2.7 ;F: 4.1 M: 6.5 ;F: 9.9 M: 14 ;F: 32	- Tubular carcinoma (1M) Tubular carcinoma (1F) Slight anemia (M) and tubular carcinoma (1F) Slight anemia (M); decreased body weight gain (M + F); Kidney weight increase (M); Tubular adenoma (6M); Tubular carcinoma (5M)

* Exposure factor was calculated by dividing the AUC_{animal} by AUC_{man}. The AUC in man was derived by multiplying the AUC of entacapone after a single (200 mg) dose (1.5 h*µg/ml) with the number of the average dosing frequency, i.e. 6 times a day.

** Rest of the female mice were sacrificed on week 95. # MC = 0.5% methyl cellulose

The mouse study did not allow for adequate assessment of the carcinogenic potential of entacapone due to the high incidence of premature mortality occurring at high doses.

In the rat two year carcinogenicity study, high doses (400 mg/kg) of entacapone caused renal adenomas and increased the number of carcinomas in male rats. The carcinogenic potential of entacapone administered in combination with levodopa/carbidopa has not been evaluated.

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PART III: CONSUMER INFORMATION

PrAURO-ENTACAPONE

Entacapone Tablets

200 mg

House Standard

This leaflet is part III of a three-part "Product Monograph" published when AURO-ENTACAPONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AURO-ENTACAPONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

AURO-ENTACAPONE tablets contain entacapone and are used together with levodopa/carbidopa or levodopa/benserazide to treat people with Parkinson's disease in whom the effect of each levodopa dose becomes shorter and who subsequently experience fluctuations in the symptoms of Parkinson's disease (end-of-dose "wearing-off").

What it does:

In Parkinson's disease the amount of dopamine is decreased in certain areas of the brain and oral levodopa is given to compensate for this decrease. Levodopa is converted to dopamine in the brain, but part of the dose of levodopa is broken down in the body to an inactive substance before it reaches the brain. AURO-ENTACAPONE helps to prevent this breakdown of levodopa, and increases the amount of levodopa that gets to the brain. When taken together with levodopa, AURO-ENTACAPONE aids levodopa in relieving the symptoms of Parkinson's disease, such as shaking of the limbs and stiffness and slowness of movement. AURO-ENTACAPONE has no effect on relieving the symptoms of Parkinson's disease unless taken with levodopa.

When it should not be used:

You should NOT take AURO-ENTACAPONE if:

- You have a history of allergic reactions to entacapone or any other components of the AURO-ENTACAPONE tablet (see "What the important nonmedicinal ingredients are").
- You have liver disease
- You are taking or have been treated in the last two weeks with certain antidepressants (both MAO-A and MAO-B inhibitors simultaneously, or non-selective MAO-inhibitors). If you are taking antidepressants and need further information, please ask your doctor or your pharmacist whether your antidepressant medication can be taken together with AURO-ENTACAPONE.
- You have a history of Neuroleptic Malignant Syndrome (NMS) (rare serious reaction to certain medicines used to treat severe mental disorders).
- You have ever suffered from rhabdomyolysis (rare form of muscle disorder) which was not caused by an injury.
- You have untreated heart, kidney, lung, blood or hormonal disease.
- You have pheochromocytoma (a tumor of the adrenal gland), because it may increase the risk of severe hypertensive reactions.
- You have been told you should not take sympathomimetic drugs such as isoproterenol, amphetamines, epinephrine or cough and cold medications containing drugs related to epinephrine.
- You have narrow angle glaucoma.
- You are pregnant (see below).
- You are breast-feeding (see below).
- You are under 18 years of age.

If you think you may be allergic, ask your doctor for advice.

If any of these apply to you, tell your doctor before taking AURO-ENTACAPONE.

What the medicinal ingredient is:

The active substance of AURO-ENTACAPONE is entacapone.

What the nonmedicinal ingredients are:

AURO-ENTACAPONE tablet contains the following Lactose monohydrate, Cellulose Microcrystalline, Mannitol, Sodium starch glycolate, croscarmellose sodium, Hydrogenated vegetable oil and magnesium stearate

Coating Ingredients:
Opadry Orange 06F530001: It contains hypromellose, titanium dioxide, macrogol , iron oxide yellow & iron oxide red.

What dosage forms it comes in:

AURO-ENTACAPONE is available in 200 mg tablets. AURO-ENTACAPONE tablets are Brownish-Orange coloured , film-coated, oval shaped tablets debossed "Y 17" on one side and plain on the other side.

WARNINGS AND PRECAUTIONS

Some people feel sleepy, drowsy, or, rarely, may suddenly fall asleep without warning (i.e. without feeling sleepy or drowsy) when taking AURO-ENTACAPONE in combination with levodopa and other drugs used to treat Parkinson's disease. Take special care when you drive or operate a machine. If you experience excessive drowsiness or a sudden sleep onset episode, refrain from driving and operating machines, and contact your physician.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. Therefore, your doctor should perform periodic skin examinations.

In a study of patients with early stage Parkinson's disease, who were treated with levodopa/carbidopa or entacapone in combination with levodopa/carbidopa for an average of about 3 years, prostate cancer was reported more frequently in the group of patients that received entacapone. It is not known if treatment with entacapone affects the risk of having prostate cancer. Therefore, it is important for men to have their regular prostate examinations during treatment with entacapone.

BEFORE you use AURO-ENTACAPONE talk to your doctor or pharmacist if:

- You have any other illnesses.
- You have ever had a heart attack or any other diseases of the heart, blood vessels or lungs.
- You have liver disease or have ever had abnormal liver function tests.
- You have severe kidney disease.
- You have ever had inflammatory bowel disease.
- You have problems urinating, or have been told you have an enlarged prostate, prostate cancer, or elevated levels of Prostate Specific Antigen (PSA).
- You have any allergies to medicines, food, dyes, or preservatives

Tell your doctor if you or your family/caregiver notices you are developing urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviors are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to review your treatments.

As **AURO-ENTACAPONE** tablets will be taken together with levodopa medicines, please also read the package leaflets of the levodopa medicines carefully.

The dose of other medicines to treat Parkinson's disease may need to be adjusted when you start taking AURO-ENTACAPONE. Follow the instructions that your doctor has given you.

Neuroleptic Malignant Syndrome (NMS) is a serious but rare reaction to certain medicines, and may occur especially when AURO-ENTACAPONE and other medicines to treat Parkinson's disease are suddenly stopped or the dose is suddenly reduced. For the symptoms of NMS see the section "Side effects and what to do about them". Your doctor may advise you to slowly discontinue the treatment with AURO-ENTACAPONE and other medicines to treat Parkinson's disease.

Driving and using machines

AURO-ENTACAPONE taken together with levodopa may lower your blood pressure, which may make you feel light-headed or dizzy. You should not drive a car or operate machinery until you are reasonably certain that AURO-ENTACAPONE does not affect your ability to carry out these activities (see precaution in box above).

Pregnancy and breast-feeding

AURO-ENTACAPONE is not to be used if you are pregnant. It is therefore important to tell your doctor immediately if you think you may have become pregnant, or are planning to become pregnant.

AURO-ENTACAPONE is not to be used if you are breast-feeding. Tell your doctor if you are breast-feeding, so that other treatment options can be tried.

Ask your doctor or pharmacist for advice before taking any medicine.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking or have recently taken any medicines, including medicines obtained without a prescription or herbal medicines. It may be necessary to change the dose, take other precautions, or perhaps stop one of the medicines. This applies to both prescription and non-prescription medicines.

In particular, tell you doctor if you are taking any of the following:

- antidepressants such as MAO inhibitors, desipramine, maprotiline, venlafaxine and paroxetine;
- warfarin used to thin the blood;
- iron supplements or multivitamins containing iron. Similar to levodopa, AURO-ENTACAPONE may impair the absorption of iron from the gastrointestinal tract. Therefore, AURO-ENTACAPONE and iron- containing medicinal products should be taken at least 2 to 3 hours apart;
- other medicines that can cause low blood pressure;
- as well as any of the following: rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine.

PROPER USE OF THIS MEDICATIONS

Follow your doctor's instructions carefully. Do not exceed the recommended dosage.

If you have any concerns about the schedule for taking your medication, talk to your doctor or pharmacist to help you sort it out.

Usual dose:

AURO-ENTACAPONE should always be used in combination with medicines containing levodopa (either levodopa/carbidopa preparations or levodopa/benserazide preparations). You may also use other medicines to treat Parkinson's disease at the same time, as advised by your doctor.

To obtain the maximum benefit from your antiparkinsonian therapy always take all medicines, including AURO-ENTACAPONE, exactly as prescribed by your doctor.

The usual dose of AURO-ENTACAPONE is one 200 mg tablet with each levodopa dose. The maximum recommended dose is 200 mg eight times a day, which is a total of 1600 mg of entacapone per day.

Your doctor will tell you exactly how many tablets of AURO-ENTACAPONE to take.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

When and how to take AURO-ENTACAPONE

AURO-ENTACAPONE can be taken with or without food. Do not break or crush the tablets.

What to expect when you start taking AURO-ENTACAPONE?

Soon after beginning and during treatment with AURO-ENTACAPONE, you may experience an increase in uncontrolled movements (dyskinesia), nausea and abdominal pain. These effects may also be more common with higher doses (1400 to 1600 mg per day) than with lower doses. This is because AURO-ENTACAPONE increases the availability of levodopa and enhances both its effectiveness and side effects. Therefore, if, for example, you notice a disturbing increase in involuntary movements (dyskinesias) after starting treatment with AURO-ENTACAPONE, you should contact your doctor for possible adjustment of your levodopa dosage to decrease the severity and frequency of these effects.

If you stop taking AURO-ENTACAPONE

DO NOT stop taking AURO-ENTACAPONE unless your doctor tells you to. When stopping, your doctor may need to re-adjust the dosage of your other medicines to treat Parkinson's disease. Suddenly stopping AURO-ENTACAPONE and other medicines to treat Parkinson's disease may result in unwanted side effects, such as severe muscular stiffness, high fever and altered consciousness.

Overdose:

If you have taken more medication than what has been prescribed, contact either a hospital emergency department, the nearest Poison Control Centre or your doctor immediately. You may require medical attention even if there are no symptoms.

Missed Dose:

If you have forgotten to take the AURO-ENTACAPONE tablet with your levodopa dose, you should continue the treatment by taking the next AURO-ENTACAPONE tablet with your next

levodopa dose. If you are unsure about what to do, consult your doctor.

Do not take a double dose of AURO-ENTACAPONE to make up for the one that you missed. If you have missed several doses, please inform your doctor immediately and follow the advice given to you.

Do not change the dose of AURO-ENTACAPONE unless instructed by your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients treated with AURO-ENTACAPONE may experience side effects, although not everybody gets them. These side effects are most likely to occur when you begin treatment with AURO-ENTACAPONE and are usually mild to moderate and rarely necessitate discontinuation of the treatment.

If you experience any of the side effects listed below, tell your doctor immediately.

Very common side effects *(affect more than 1 patient in 10)*

- Uncontrollable movements with difficulty in performing voluntary movements (dyskinesias);
- feeling sick (nausea);
- harmless reddish-brown discoloration of urine. AURO-ENTACAPONE may also cause darkening of sweat and saliva.

Common side effects *(affect 1 to 10 patients in 100)*

- Excessive movements of the body (hyperkinesias);
- headache;
- fever;
- tremor;
- prolonged muscle cramps (dystonia), leg cramps;
- hallucinations (seeing/hearing/feeling/smelling things that are not really there), confusion;
- heart or artery disease events other than a heart attack (e.g., chest pain, swelling or blue coloration of the extremities, shortness of breath on exertion, angina, disease of the heart valves or other conditions identified by your physician);
- worsening of symptoms of Parkinson's disease;
- being sick (vomiting), diarrhea, abdominal pain, constipation, dry mouth;
- decrease in blood pressure when standing up rapidly after sitting or lying down, with or without symptoms such as dizziness or light headedness, increased sweating, falling, fainting;
- dizziness, tiredness, increased sweating, falling;
- vertigo (sensation of spinning or whirling motion);
- sleeplessness, nightmares.

Uncommon (*affects 1 to 10 patients in 1,000*)

- Heart attack (chest pain often associated with left shoulder or jaw pain, feeling of constriction around chest and sweating).

Rare side effects *(affect 1 to 10 patients in 10,000)*

- Abnormal results in liver function tests.

Very rare side effects *(affect less than 1 patient in 10,000)*

- Inflammation of the colon (colitis) which may cause severe diarrhea or weight loss;
- agitation;
- decreased appetite, weight loss;
- hives;
- discoloration of the skin, hair, beard and nails;
- Excessive daytime sleepiness and sleep onset episodes;
- Neuroleptic Malignant Syndrome (NMS), which can cause symptoms of stiffness, muscle twitching, shaking, agitation, confusion, coma, high body temperature, increased heart rate, and unstable blood pressure;
- inflammation of the liver (hepatitis), which can cause increasing loss of appetite, weakness, exhaustion, weight loss in a relatively short period of time, yellowing of your skin, hair, nail, or the white of your eyes, dark colored urine;
- serious skin reactions (rash that might be severe, red skin, blistering of the lips, eyes or mouth, peeling skin).
- severe muscle disorder (rhabdomyolysis) which causes pain, tenderness and weakness of the muscles and may lead to kidney problems;
- allergic reactions (symptoms may include redness, itching, rash, swelling of your skin, hives, swelling around the eyes, lips; swelling of hands, feet, face, tongue or throat; any trouble breathing or swallowing not present before using this medicine).

Together with levodopa, AURO-ENTACAPONE may lower your blood pressure and cause postural (orthostatic) hypotension (a decrease in your blood pressure when standing up rapidly after sitting or lying down), with or without symptoms such as

dizziness, nausea, syncope (fainting) and sweating. Hypotension may occur more frequently during the start of treatment with AURO-ENTACAPONE. Therefore, you should avoid standing rapidly after sitting or lying down, especially after prolonged periods. You should also be careful if you are taking other medicinal products which may cause dizziness or light-headedness (low blood pressure) when rising from a chair or bed.

Severe diarrhea while taking AURO-ENTACAPONE can cause significant loss of weight for some individuals. In some cases diarrhea and weight loss have been caused by inflammation of the colon that occurred during treatment with entacapone. Therefore, it is important to tell your doctor if you have diarrhea so that the cause of your symptoms can be determined. Your weight should also be closely monitored. Your treatment may need to be adjusted to avoid diarrhea and excessive weight loss.

If you experience increasing loss of appetite, weakness, exhaustion and weight loss in a relatively short period of time after starting treatment with entacapone, contact your doctor. He/she may decide to do a general medical evaluation, including blood tests to check liver function.

Abnormal results of blood tests, such as decrease in red blood cells, have been observed in people taking entacapone.

AURO-ENTACAPONE may also cause other adverse events. If you have any questions or concerns about these effects you should talk to your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Hallucinations (seeing/hearing/feeling/smelling things that are not really there)		√	
	Diarrhea		√	
	Decrease in blood pressure when standing up rapidly after sitting or lying down, with or without symptoms such as dizziness or light headedness, increased sweating, falling, fainting		√	
	Heart or artery disease events other than a heart attack (e.g., chest pain, swelling or blue coloration of the extremities, shortness of breath on exertion, angina, disease of the heart (valves)			√
Uncommon	Heart attack (chest pain often associated with left shoulder or jaw pain, feeling of constriction around chest and sweating)			√
	Inability to control impulse to perform an action		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist right away**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
	that could be harmful, such as: strong impulse to gamble excessively, altered or increased sexual interest and behavior of significant concern to you or to others, uncontrollable excessive shopping or spending, binge eating or compulsive eating.			
Very rare	Excessive daytime sleepiness, drowsiness, suddenly falling asleep		√	
	Neuroleptic Malignant Syndrome NMS) (stiffness, muscle twitching, shaking, agitation, confusion, coma, high body temperature, increased heart rate, and unstable blood pressure)			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist right away**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
	Inflammation of the liver (hepatitis) which can cause increasing loss of appetite, weakness, exhaustion, weight loss in a relatively short period of time, yellowing of your skin, hair, nail, or the white of the eyes, dark colored urine			√
	Serious skin reactions (rash that might be severe, red skin, blistering of the lips, eyes or mouth, peeling skin)			√
	Rhabdomyolysis (pain, tenderness weakness of the muscles)			√
	Allergic reactions (symptoms may include redness, itching, rash, swelling of your skin, hives, swelling around the eyes, lips; swelling of hands, feet, face, tongue or throat; any trouble breathing or swallowing not			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	present before using this medicine)			

This is not a complete list of side effects. For any unexpected effects while taking AURO-ENTACAPONE, contact your doctor or pharmacist.

HOW TO STORE IT

- Store at room temperature (15ºC -30ºC).
- Do not take AURO-ENTACAPONE past the expiry date shown on the bottle or carton labels.
- Do not use if the package is damaged or shows signs of tampering.
- Keep out of the sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full Product Monograph, prepared for health professionals can be found at:

http:// www.auropharma.ca or by contacting the sponsor, Auro Pharma Inc., at: 1-855-648-6681

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