

COMTAN (entacapone) 200mg Tablets

DESCRIPTION: COMTAN[®] is available as tablets containing 200-mg entacapone.

Entacapone is an inhibitor of catechol-*O*-methyltransferase (COMT), used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. It is a nitrocatechol-structured compound with a relative molecular mass of 305.29. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is C₁₄H₁₅N₃O₅ and its structural formula is:

The inactive ingredients of the COMTAN tablet are microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red oxide, and titanium dioxide

CLINICAL PHARMACOLOGY:

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

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa, catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When entacapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels 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: COMT Activity in Erythrocytes: Studies in healthy volunteers have shown that entacapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. There was a linear correlation between entacapone dose and erythrocyte COMT inhibition, the maximum inhibition being 82% following an 800-mg single dose. With a 200-mg single dose of entacapone, maximum inhibition of erythrocyte COMT activity is on average 65% with a return to baseline level within 8 hours.

COMTAN (entacapone) 200mg Tablets

Effect 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 2.4h. 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. Studies in Parkinson's disease patients suggest that the maximal effect occurs with 200-mg entacapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by entacapone when given with levodopa/carbidopa.

Pharmacokinetics of Entacapone: Entacapone pharmacokinetics are linear over the dose range of 5 to 800 mg, and are independent of levodopa/carbidopa coadministration. The elimination of entacapone is biphasic, with an elimination half-life of 0.4 to 0.7 h based on the β -phase and 2.4 h based on the γ -phase. The γ -phase accounts for approximately 10% of the total AUC. The total body clearance after i.v. administration is 850 ml/min. After a single 200-mg dose of COMTAN, the C_{max} is approximately 1.2 μ g/mL.

Absorption: Entacapone is rapidly absorbed, with a T_{max} of approximately 1 hour. The absolute bioavailability following oral administration is 35%. Food does not affect the pharmacokinetics of entacapone.

Distribution: The volume of distribution of entacapone at steady state after i.v. Injection is small (20 L). 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 μ g/mL. Entacapone binds mainly to serum albumin.

Metabolism and Elimination: Entacapone is almost completely metabolized prior to excretion, with only a very small amount (0.2 % of dose) found unchanged in urine. The main metabolic pathway is isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer; the glucuronide conjugate is inactive. After oral administration of a 14 C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Special Populations: 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 COMTAN on groups other than Caucasian.

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

Renal Impairment: The pharmacokinetics of entacapone have been investigated after a single 200-mg entacapone dose, without levodopa/dopa decarboxylase inhibitor coadministration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12

COMTAN (entacapone) 200mg Tablets

ml/sec/1.73 m²) moderate impairment (n=10; creatinine clearance ranging from 0.60 to 0.89 ml/sec/1.73 m²), and severe impairment (n=7; creatinine clearance ranging from 0.20 to 0.44 ml/sec/1.73 m²),). No important effects of renal function on the pharmacokinetics of entacapone were found.

Drug Interactions: See PRECAUTIONS: *Drug Interactions.*

Clinical Studies

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

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

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

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

The following tables display the results of these two trials

COMTAN (entacapone) 200mg Tablets

Table 1. Nordic Study

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

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

At least one category change at endpoint. *Not significant

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

COMTAN (entacapone) 200mg Tablets

Table 2. North American Study

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

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

**At least one category change at endpoint. I Not significant

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

10/19/99 APPROVAL LABEL

NDA 20-796

PAGE 6

COMTAN (entacapone) 200mg Tablets

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

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

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

COMTAN (entacapone) 200mg Tablets

Table 3. German-Austrian Study

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

* Total population; score change at endpoint

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

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

COMTAN (entacapone) 200mg Tablets

INDICATIONS: COMTAN is indicated as an adjunct to levodopa / carbidopa 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*).

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

CONTRAINDICATIONS: COMTAN tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS:

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of COMTAN and a non-selective MAO inhibitor (e.g., phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with COMTAN and a non-selective MAO inhibitor.

Entacapone can be taken concomitantly with a selective MAO-B inhibitor (e.g., selegiline).

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/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isotherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

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

PRECAUTIONS:

Hypotension/Syncope: Dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension. Entacapone enhances levodopa bioavailability and, therefore, might be expected to increase the occurrence of orthostatic hypotension. In COMTAN clinical trials, however, no differences from placebo were seen for measured orthostasis or symptoms of orthostasis. Orthostatic hypotension was documented at least once in 2.7 % and 3.0 % of the patients treated 200 mg COMTAN and placebo respectively. A total of 4.3 % and 4.0 % of the patients treated with 200 mg COMTAN and placebo, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was not accompanied by vital sign measurements). Neither baseline treatment

COMTAN (entacapone) 200mg Tablets

with dopamine agonists or selegiline, nor the presence of orthostasis at baseline, increased the risk of orthostatic hypotension in patients treated with COMTAN compared to patients on placebo.

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

Diarrhea: In clinical trials, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg COMTAN and placebo, respectively. In patients treated with COMTAN diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, (1.2%) with mild and moderate diarrhea and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of COMTAN. Two patients with diarrhea were hospitalized. 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.

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 COMTAN or placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8 % and 0% of patients treated with 200 mg COMTAN and placebo, respectively. Hallucinations led to hospitalization in 1.0 % and 0.3 % of patients in the 200 mg COMTAN and placebo groups, respectively.

Dyskinesia: COMTAN 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 COMTAN and placebo, respectively.

Other Events Reported With Dopaminergic Therapy: The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists:

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

Hyperpyrexia and Confusion: Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. Several cases with similar signs and symptoms have been reported in association with COMTAN therapy, although no information about dose manipulation is available. The complicated nature of these cases makes it difficult to determine what role, if any, Comtan may have played in their

COMTAN (entacapone) 200mg Tablets

pathogenesis. No cases have been reported following the 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 COMTAN, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering COMTAN has not been systematically evaluated.

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

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.

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

Information for Patients: Patients should be instructed to take COMTAN only as prescribed.

Patients should be informed that hallucinations can occur.

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

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

COMTAN (entacapone) 200mg Tablets

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

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

Patients should be advised that treatment with entacapone may cause a change in the color of their urine (a brownish orange discoloration) that is not clinically relevant. In controlled trials, 10% of patients treated with COMTAN reported urine discoloration compared to 0% of placebo patients.

Although COMTAN has not been shown to be teratogenic in animals, it is always given in conjunction with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS: *Pregnancy*).

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

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

Special Populations: Patients with hepatic impairment should be treated with caution (see INDICATIONS, DOSAGE AND ADMINISTRATION).

Drug Interactions: *In vitro* studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A only at very high concentrations (IC₅₀ from 200 to over 1000 μ M; an oral 200 mg dose achieves a highest level of approximately 5 μ M in people); these enzymes would therefore not be expected to be inhibited in clinical use.

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

Drugs Metabolized by Catechol-O-methyltransferase (COMT): (See WARNINGS)

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

Effect of Entacapone on the Metabolism of Other Drugs: See WARNINGS regarding concomitant use of COMTAN and non-selective MAO inhibitors.

No interaction was noted with the MAO-B inhibitor selegiline in two multiple-dose interaction studies when entacapone was coadministered with a levodopa/dopa decarboxylase inhibitor (n=29). More than

COMTAN (entacapone) 200mg Tablets

600 Parkinson's disease patients in clinical trials have used selegiline in combination with entacapone and levodopa/dopa decarboxylase inhibitor.

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

No interaction with the tricyclic antidepressant imipramine was shown in a single-dose study with entacapone without coadministered levodopa/dopa-decarboxylase inhibitor.

Carcinogenesis: Two-year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400 mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600 mg). Mice were treated once daily by oral gavage with doses of 20, 100 or 600 mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m² basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with levodopa/carbidopa has not been evaluated.

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).

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

Pregnancy: Pregnancy Category C. In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of 1600 mg. 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 MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in

COMTAN (entacapone) 200mg Tablets

humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

Entacapone is always given concomitantly with Sinemet, which is known to cause visceral and skeletal malformations in rabbits. The teratogenic potential of entacapone in combination with Sinemet was not assessed in animals.

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

Nursing Women: In animal studies, entacapone was excreted into maternal rat milk.

It is not known whether entacapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when entacapone is administered to a nursing woman.

Pediatric Use: There is no identified potential use of entacapone in pediatric patients.

ADVERSE REACTIONS:

During the pre-marketing development of entacapone, 1450 patients with Parkinson's Disease were treated with entacapone. Included were patients with fluctuating symptoms, as well as those with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects.

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

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

COMTAN (entacapone) 200mg Tablets

Adverse Event Incidence in Controlled Clinical Studies: Table 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double-blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to levodopa/carbidopa (or levodopa/benserazide).

Table 4. Summary of Patients with Adverse Events after Start of Trial Drug Administration At least 1 % in COMTAN group and > Placebo

SYSTEM ORGAN CLASS Preferred term	COMTAN (n = 603) % of patients	Placebo (n = 400) % of patients
SKIN AND APPENDAGES DISORDERS		
Sweating increased	2	1
MUSCULO-SKELETAL SYSTEM DISORDERS		
Back pain	2	1
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dyskinesia	25	15
Hyperkinesia	10	5
Hypokinesia	9	8
Dizziness	8	6
SPECIAL SENSES OTHER, DISORDERS		
Taste perversion	1	0
PSYCHIATRIC DISORDERS		
Anxiety	2	1
Somnolence	2	0
Agitation	1	0
GASTRO-INTESTINAL SYSTEM DISORDERS		
Nausea	14	8
Diarrhea	10	4
Abdominal pain	8	4
Constipation	6	4
Vomiting	4	1
Mouth dry	3	0
Dyspepsia	2	1
Flatulence	2	0
Gastritis	1	0
Gastro-intestinal disorders nos	1	0
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	3	1
PLATELET, BLEEDING & CLOTTING DISORDERS		
Purpura	2	1
URINARY SYSTEM DISORDERS		
Urine discoloration	10	0
BODY AS A WHOLE – GENERAL DISORDERS		
Back pain	4	2
Fatigue	6	4
Asthenia	2	1
RESISTANCE MECHANISM DISORDERS		
Infection bacterial	1	0

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from

COMTAN (entacapone) 200mg Tablets

those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

Effects of gender and age on adverse reactions: No differences were noted in the rate of adverse events attributable to entacapone by age or gender.

DRUG ABUSE AND DEPENDENCE: Entacapone is not a controlled substance. Animal studies to evaluate the drug abuse and potential dependence have not been conducted. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

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

The highest single dose of entacapone administered to humans was 800 mg, resulting in a plasma concentration of 14.1 ug/ml. The highest daily dose given to humans was 2400 mg, administered in one study as 400 mg six times daily with levodopa/carbidopa for 14 days in 15 Parkinson's disease patients, and in another study as 800 mg tid for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0 µg/mL (at 45 min, compared to 1.0 and 1.2 µg/mL with 200 mg entacapone at 45 min). Abdominal pain and loose stools were the most commonly observed adverse events during this study. Daily doses as high as 2000 mg COMTAN have been administered as 200 mg 10 times daily with levodopa/carbidopa or levodopa/benserazide for at least 1 year in 10 patients, for at least 2 years by 8 patients and for at least 3 years in 7 patients. Overall, however, clinical experience with daily doses above 1600 mg is limited.

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

Management of Overdose: Management of COMTAN overdose is symptomatic; there is no known antidote to COMTAN. Hospitalization is advised, and general supportive care is indicated. There is no experience with hemodialysis or hemoperfusion, but these procedures are unlikely to be of benefit, because COMTAN is highly bound to plasma proteins. An immediate gastric lavage and repeated doses of charcoal over time may hasten the elimination of COMTAN by decreasing its absorption/reabsorption from the GI tract. The adequacy of the respiratory and circulatory systems should be carefully monitored and appropriate supportive measures employed. The possibility of drug interactions, especially with catechol-structured drugs, should be borne in mind.

DOSAGE AND ADMINISTRATION: The recommended dose of COMTAN is one 200 mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily (200 mg x 8 = 1600 mg per day). Clinical experience with daily doses above 1600 mg is limited.

COMTAN should always be administered in association with levodopa/carbidopa. Entacapone has no antiparkinsonian effect of its own.

COMTAN (entacapone) 200mg Tablets

In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa had been ≥ 800 mg, or if patients had moderate or severe dyskinesias before beginning treatment.

To optimize an individual patient's response, reductions in daily levodopa dose or extending the interval between doses may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 25 % in those patients requiring a levodopa dose reduction. (More than 58 % of patients with levodopa doses above 800 mg daily required such a reduction.)

COMTAN can be combined with both the immediate and sustained release formulations of levodopa/carbidopa.

COMTAN may be taken with or without food (see CLINICAL PHARMACOLOGY).

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

Withdrawing Patients from COMTAN: Rapid withdrawal or abrupt reduction in the COMTAN dose could lead to emergence of signs and symptoms of Parkinson's disease (see CLINICAL PHARMACOLOGY, Clinical Trials), and may lead to Hyperpyrexia and Confusion, a symptom complex resembling the neuroleptic malignant syndrome (see PRECAUTIONS: *Events Reported With Dopaminergic Therapy*). This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. If a decision is made to discontinue treatment with COMTAN, patients should be monitored closely and other dopaminergic treatments should be adjusted as needed. Although tapering COMTAN has not been systematically evaluated, it seems prudent to withdraw patients slowly if the decision to discontinue treatment is made.

10/19/99 APPROVAL LABEL

NDA 20-796

PAGE 17

COMTAN (entacapone) 200mg Tablets

HOW SUPPLIED: COMTAN is supplied as 200-mg film-coated tablets for oral administration. The oval-shaped tablets are brownish-orange, unscored, and embossed “COMTAN” on one side. Tablets are provided in HDPE containers as follows:

Bottles of 10 (NDC 0078-9327-01)

Bottles of 100 (NDC 0078-0327-05)

Bottles of 500 (NDC 0078-0327-08).

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

COMTAN (entacapone) Tablets are manufactured by Orion Corporation, Orion Pharma (Espoo, Finland) and marketed by Novartis Pharmaceuticals Corporation (East Hanover, N.J. 07936, USA).