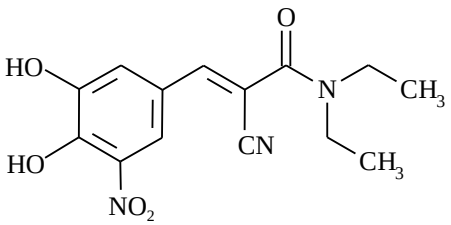
# COMTAN®
**entacapone**

## NAME OF THE MEDICINE

INN: Entacapone

Structural Formula:




Chemical name: (*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethyl-2-propenamide

Molecular formula: $C_{14}\ H_{15}\ N_3\ O_5$

Molecular weight: 305.28

CAS number: 130929-57-6

## DESCRIPTION

Entacapone is a yellow or greenish yellow crystalline powder. The (*E*)-isomer is the main product and less than 0.5% of the (*Z*)-isomer occurs in the raw material. Comtan is available as film coated tablets, each containing 200 mg of entacapone.

Excipients: cellulose-microcrystalline, mannitol, croscarmellose sodium, vegetable oil-hydrogenated, hypromellose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, iron oxide yellow CI77492, iron oxide red CI77491, titanium dioxide.

## PHARMACOLOGY

### Pharmacokinetics

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

**Absorption:**

The peak concentration ($C_{max}$) of entacapone in plasma is usually reached about one hour after ingestion of a 200 mg tablet of Comtan. The drug is subject to extensive first-pass metabolism. The bioavailability of entacapone is about 35% after an oral dose. Food does not affect the absorption of entacapone to any significant extent, but the effects of a fatty meal on its absorption have not been studied.

**Distribution:**

After absorption from the gastrointestinal tract, entacapone is rapidly distributed to the peripheral tissues, with a distribution volume at steady state of 20 L. Entacapone is extensively bound to plasma proteins, mainly to albumin. Within the range of therapeutic concentrations, the unbound fraction in human plasma is about 2.0%.

**Metabolism and elimination:**

A small amount of entacapone, the *(E)*-isomer, is converted to its *(Z)*-isomer. The *(E)*-isomer accounts for 95% of the AUC of entacapone. The *(Z)*-isomer and traces of other metabolites account for the remaining 5% of AUC.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 ($IC_{50}$ ~4 μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19)[see "PRECAUTIONS - Interactions with Other Drugs"].

The elimination of entacapone occurs mainly by non-renal metabolic routes. Entacapone is metabolised in the liver primarily by conjugation with glucuronic acid. The elimination of entacapone occurs mainly by biliary excretion. About 10% of the dose is excreted in the 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.

Approximately 92% of the dose is eliminated during the β-phase with a short elimination half-life of 30 minutes. The total plasma clearance of entacapone is about 800 ml/min. There is no evidence of polymorphic metabolism of entacapone.

**Pharmacokinetics in the elderly:**

The pharmacokinetic properties of entacapone are similar in both young and elderly adults.

**Pharmacokinetics in patients with hepatic dysfunction:**

The metabolism of entacapone is slowed in patients with mild to moderate liver impairment (Child-Pugh Class A and B), which leads to an increased plasma concentration of entacapone, both in the absorption and elimination phases (see "CONTRAINDICATIONS").

**Pharmacokinetics in patients with renal dysfunction:**

Renal impairment does not affect the pharmacokinetics of entacapone and there is no need for dose adjustment. However, the possible need for a longer dosing interval should be kept in mind in the treatment of patients receiving dialysis therapy (see "DOSAGE AND ADMINISTRATION").

**Pharmacodynamics**

Entacapone belongs to a new therapeutic class, the catechol-*O*-methyl transferase (COMT) inhibitors. It is a reversible, specific, and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa preparations. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the enzyme COMT. This leads to a more sustained plasma concentration of levodopa with no delay in the time to reach the peak concentration. The amount of levodopa available to the brain is increased and more dopamine is formed in the central nervous system. Entacapone thus prolongs the clinical response to levodopa.

Entacapone inhibits the enzyme COMT mainly in peripheral tissues. COMT inhibition in red blood cells closely follows the plasma concentration of entacapone, thus clearly indicating the reversible nature of COMT inhibition. The antiparkinsonian effects of entacapone, i.e. the effects of entacapone on levodopa pharmacokinetics, have nearly disappeared 24 hours after stopping drug intake.

## CLINICAL TRIALS

The use of Comtan in the treatment of patients with Parkinson's disease was supported by the results of one pivotal Phase II and two pivotal Phase III studies. The majority of patients also suffered from fluctuations in motor performance. All patients were treated concomitantly with a levodopa/dopa decarboxylase (DDC) inhibitor and the patients were also permitted to use other antiparkinsonian drugs.

The pivotal efficacy studies recruited only patients with motor fluctuations. To avoid any confounding factors in the use of controlled release levodopa, patients were switched to immediate release preparations. Although clinical pharmacology studies have shown that entacapone increases the bioavailability of levodopa from controlled release formulations, efficacy in patients has not been proven. Although patients without motor fluctuations have not been systematically evaluated for efficacy, they have been included in the placebo controlled and open-label safety studies.

A pivotal double-blind Phase II study was completed in 23 patients with advanced Parkinson's disease. Subjects received 4 weeks of treatment with Comtan and 4 weeks of placebo in a cross-over format. A tablet of Comtan 200 mg or placebo was administered with each scheduled dose of levodopa/DDC inhibitor four to ten times daily during each treatment period. The primary efficacy parameter was the change in the duration of motor response ("ON" time), as scored on the modified motor part of the UPDRS (Unified Parkinson's Disease Rating Scale). Using measurements taken every 30 minutes for 4 to 6 hours at the end of the treatment periods, Comtan was found to increase the mean "ON" time significantly relative to placebo ($p<0.01$). The mean total daily levodopa dosage required by the patients was decreased by 140 mg in the Comtan group relative to placebo ($p<0.01$).

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

In both studies, Comtan had a significant positive effect on the primary, and most of the secondary, efficacy parameters. In the NOMECOMT study, the mean daily "ON" time was 1.3 hours (approximately 14%) longer in the Comtan group relative to placebo ($p<0.001$). The percent of "ON" time while awake increased significantly ($p<0.001$) and the duration of "ON" time after the first daily dose was also significantly longer ($p<0.05$). In the SEESAW

study, although the increase in daily "ON" time of 0.6 hours did not reach statistical significance, the "ON" time expressed as a percent of time awake was significantly improved ($p<0.05$). The UPDRS objective disease rating (total, activities of daily living, motor parts) and the global evaluation by the investigator were significantly in favour of Comtan in both studies, and the daily dose of levodopa required decreased by approximately 100 mg per day ($p<0.001$).

At the end of the active treatment period, a well defined withdrawal effect of Comtan was demonstrated, with the outcome for all variables showing a significant deterioration in the patients' condition. The average daily "ON" time decreased by 1.5 hours ($p<0.001$) and the motor score of the UPDRS deteriorated significantly ($p<0.01$) in both studies.

Additional data on the safety of entacapone has been obtained from approximately 800 patients treated for 1 year and about 400 patients treated for at least 2 years.

# INDICATIONS

Comtan is indicated in the management of Parkinson's disease as an adjunct to levodopa/dopa decarboxylase inhibitor therapy in patients who are experiencing motor fluctuations (see "Clinical Trials").

# CONTRAINDICATIONS

- Known hypersensitivity to entacapone or any other components of the formulation.
- Pregnancy and breast feeding (see "PRECAUTIONS - Use in Pregnancy and Use in Lactation")
- Hepatic impairment (see "PHARMACOLOGY – Pharmacokinetics")
- Patients with phaeochromocytoma due to the increased risk of hypertensive crisis.
- Concomitant use of Comtan with non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine) is contraindicated. Similarly, concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and Comtan is contraindicated.
- A previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

# PRECAUTIONS

## Use with Caution in the Following Circumstances

**Neuroleptic malignant syndrome and rhabdomyolysis:**

Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has been observed rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment.

NMS, including rhabdomyolysis and hyperthermia, is characterised by motor symptoms (rigidity, myoclonus, tremor), changes in mental status (e.g. agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum

creatine phosphokinase (CPK). In individual cases, only some of these symptoms and/or findings may be evident.

Isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of Comtan and other dopaminergic medications. When considered necessary, withdrawal of Comtan and other dopaminergic treatment should proceed slowly and, if signs and/or symptoms occur despite a slow withdrawal of Comtan, an increase in levodopa dosage may be necessary.

**Ischaemic heart disease:**

Entacapone therapy should be administered with caution to patients with ischaemic heart disease.

**Diarrhoea, anorexia, asthenia and weight loss:**

For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhoea suspected to be related to entacapone may be a sign of colitis. In the event of prolonged or persistent diarrhoea, entacapone should be discontinued and appropriate medical therapy and investigations considered.

For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.

**Impulse control disorders:**

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as entacapone in association with levodopa. Review of treatment is recommended if such symptoms develop.

**Use in combination with levodopa:**

Comtan is always given as an adjunct to levodopa treatment. Hence, the precautions applicable to levodopa treatment should also be taken into account for Comtan treatment.

Entacapone may aggravate levodopa-induced orthostatic hypotension. Comtan should be given cautiously to patients who are taking other medications that may cause orthostatic hypotension.

Comtan in association with levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease. Therefore, caution should be exercised when driving or operating machinery (see "PRECAUTIONS-Effects on ability to drive or operate machinery").

**Use in combination with other antiparkinsonian medications:**

In clinical studies, undesirable dopaminergic effects (e.g. dyskinesia) were more common in patients who received Comtan and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to patients who received placebo in combination with any of these medications. The doses of other antiparkinsonian medications may require adjustment when Comtan treatment is initiated.

**Interactions with other drugs**

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 Comtan is added to levodopa/benserazide treatment. To reduce levodopa-related dopaminergic adverse reactions, it is often necessary to adjust levodopa dosage within the first days to weeks after initiating Comtan treatment, according to the clinical condition of the patient (see "DOSAGE AND ADMINISTRATION" and "ADVERSE EFFECTS").

High single doses (≥400 mg) of entacapone may decrease the bioavailability of carbidopa. However, no interaction of entacapone with carbidopa has been observed with the recommended dosage schedule. Pharmacokinetic interaction with benserazide has not been studied.

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

Due to its inhibitory effect on cytochrome P450 2C9 activity (see "Pharmacokinetics – Metabolism and elimination"), entacapone may potentially interfere with drugs whose metabolism is dependent on this isoenzyme, such as warfarin, which is commercially available as a racemic mixture of the S(-) and R(+) enantiomers of the sodium salt. 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% [$CI_{90}$ 11-26%]. The International Normalised Ratio (INR) values increased on average by 13% [$CI_{90}$ 6-19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

In single-dose studies in healthy volunteers, no interactions were observed between entacapone and imipramine, or between entacapone and moclobemide. Similarly, no interactions were observed between entacapone and selegiline in repeated-dose studies in patients with Parkinson's disease. Comtan may be used in combination with selegiline (a selective MAO-B inhibitor), but the daily dose of selegiline should not exceed 10 mg.

However, experience of the clinical use of entacapone with several drugs, including MAO-A inhibitors (see "CONTRAINDICATIONS"), tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine and venlafaxine, and drugs containing a catechol group that are metabolised by COMT (see below), is still limited. Concomitant use of Comtan with these drugs is not recommended.

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

Entacapone may form chelates with iron in the gastrointestinal tract. Comtan and iron preparations should be taken at least 2 – 3 hours apart (see "ADVERSE EFFECTS").

**Sucrose:**

Comtan tablets contain sucrose. Therefore, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**Effects on ability to drive or operate machinery:**

Comtan on its own is not expected to impair the ability to drive or to operate machinery. However, it may increase some side effects of levodopa, such as dizziness, somnolence and episodes of sudden sleep onset, and symptomatic orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. The ability of patients with Parkinson's disease to drive or operate machinery should be evaluated by the treating physician.

Comtan in association with levodopa may have major influence on the ability to drive and use machines. Patients being treated with Comtan 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 "PRECAUTIONS-Use in combination with levodopa").

**Use in children:**

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

**Use in Pregnancy (Pregnancy Category B3)**

No teratogenicity was observed following administration of entacapone to pregnant rats and rabbits during the period of organogenesis at oral doses producing respective maternal exposures (plasma AUC) of 40 times, and marginally greater than, the maximal clinical exposure. In pregnant rabbits, fetotoxicity and abortions occurred at maternal exposures less than the maximal clinical exposure. The extent of placental transfer of entacapone and its metabolites in animals and humans is unknown, and there is no experience of the use of Comtan in pregnant women. The use of this drug during pregnancy is not recommended.

**Use in Lactation**

In lactating rats, entacapone and/or its metabolites are excreted into milk. Oral administration of entacapone to rats from early pregnancy to weaning reduced offspring body weight at maternal exposure (plasma AUC) of 26 times the maximal clinical exposure, but not at an exposure of 6 times the maximal clinical exposure. It is not known whether entacapone is excreted in human milk and Comtan is, therefore, not recommended for nursing mothers.

**Carcinogenicity, mutagenicity, impairment of fertility:**

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

Entacapone was not genotoxic in a bacterial gene mutation assay, but positive results were obtained in a mammalian gene mutation assay and an in vitro assay for clastogenicity. An in

vivo assay for clastogenicity and assays for DNA damage were negative.

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

## ADVERSE EFFECTS

The most frequent adverse events caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of treatment. Reduction of levodopa dosage may decrease the severity and frequency of these events. The other major class of adverse events are gastrointestinal symptoms, including nausea, vomiting, abdominal pains, constipation and diarrhoea. Due to the presence of a nitrocathecholamine group in the molecule, urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.

Usually adverse events caused by entacapone are mild to moderate. Most commonly the adverse events leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea) and dopaminergic symptoms (e.g. dyskinesias).

Comtan in association with levodopa has been associated with isolated episodes of excessive daytime somnolence and sudden sleep onset.

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

Isolated cases of rhabdomyolysis have been reported.

Impulse control disorders: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as entacapone in association with levodopa (see 'PRECAUTIONS – Impulse control disorders').

Table 1: Adverse events reported with a frequency of ≥ 3% in double-blind placebo controlled phase III studies of entacapone.

| Body system | Entacapone % (n = 603) | Placebo % (n = 400) |
|---|---|---|
| **Autonomic nervous system:** | | |
| Hypotension - postural | 2.7 | 3.0 |
| **Body as a whole:** | | |
| Fatigue | 6.1 | 3.5 |
| Pain | 6.0 | 4.5 |
| Back pain | 5.0 | 3.0 |
| Headache | 3.5 | 4.3 |
| Falls | 4.1 | 3.5 |
| Sweating increased | 3.6 | 3.0 |
| **Gastrointestinal system:** | | |
| Nausea | 13.8 | 7.5 |
| Diarrhoea | 10.0 | 4.0 |
| Abdominal pain | 8.1 | 4.5 |

| | | |
|---|---|---|
| Constipation | 6.3 | 4.3 |
| Vomiting | 4.0 | 1.0 |
| Dry mouth | 3.0 | 0.3 |
| **Nervous system:** | | |
| Dyskinesia | 25.2 | 14.8 |
| Parkinsonism aggravated | 13.9 | 14.8 |
| Hyperkinesia | 9.5 | 5.0 |
| Hypokinesia | 8.6 | 7.5 |
| Dizziness | 7.5 | 6.0 |
| Tremor | 5.0 | 6.5 |
| Dystonia | 3.0 | 4.3 |
| Leg cramps | 3.0 | 3.5 |
| Vertigo | 2.3 | 3.3 |
| **Psychiatric disorders:** | | |
| Insomnia | 6.3 | 7.3 |
| Hallucinations | 4.1 | 4.0 |
| Depression | 3.2 | 3.3 |
| **Urinary system:** | | |
| Urine colour abnormal | 9.5 | 0.0 |

Dyskinesias, nausea, diarrhoea, abdominal pain and dry mouth were reported significantly more often with entacapone than with placebo (see Table 1). Other common adverse events (incidence < 3%) included sleep disturbances and paroniria. Serious adverse events (incidence > 0.3% and ≥ placebo) that do not appear in Table 1 included chest pain, pneumonia, confusion and dyspnoea.

Some of the adverse events, such as dyskinesia, nausea, and abdominal pains, may be more common with the higher doses (1400 to 2000 mg per day) than with the lower doses of entacapone.

**Adverse effects in laboratory tests:**

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

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

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

placebo (carbidopa/levodopa) patients who experienced myocardial infarction in the double-blind wearing-off studies.

**Post-marketing reports:**

Adverse reactions are ranked under headings of frequency using the following convention: Very common (≥10%); common (≥1% to <10%); uncommon (≥0.1% to <1%); rare (≥0.01% to <0.1%); very rare (<0.01% including isolated reports).

**Body as a whole:**
Very rare: weight decrease
**Dermatological disorders:**
Rare: erythematous or maculopapular rash
Very rare: urticaria, skin, hair, beard and nail discolourations
**Gastrointestinal disorders**
Very rare: anorexia, colitis
**Hepatic disorders:**
Rare: hepatic function tests abnormal
Very rare: hepatitis with cholestatic features
**Psychiatric disorders:**
Common: confusion, nightmares
Very rare: agitation
**Cardiac disorders:**
Common: ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris)
Uncommon: myocardial infarction

## DOSAGE AND ADMINISTRATION

Comtan is used in combination with levodopa preparations, either levodopa/carbidopa or levodopa/benserazide. It can be used with both standard and sustained-release preparations of levodopa. Other antiparkinsonian drugs may be used simultaneously.

Entacapone enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reactions (e.g. dyskinesias, nausea, vomiting and hallucinations) it is often necessary to adjust levodopa dosage within the first few days to first few weeks after initiating treatment with Comtan. The daily dose of levodopa should be reduced by about 10 to 30% by extending the dosing intervals and/or by reducing the amount of levodopa per dose.

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

If Comtan treatment is discontinued, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms.

**Comtan Dosage Regimen**

**Starting dose:** one 200 mg tablet is taken with each levodopa/dopa decarboxylase inhibitor dose. On average 4 to 7 doses daily are used in patients with moderate or severe Parkinson's disease. The same dosage is used in all adults, including elderly patients. Comtan may be taken with or without food. The effects of a high fat meal on absorption have not been formally evaluated.

**Maintenance dose: The maintenance dose of Comtan is the same as the starting dose.**

**Maximum recommended dose:** 2000 mg (i.e. 10 doses) daily.

**Patients with renal dysfunction:** renal insufficiency does not affect the pharmacokinetics of entacapone and there is no need for dose adjustment. However, patients who are receiving dialysis therapy should be closely monitored and the possible need for a longer dosing interval should be kept in mind.

## OVERDOSAGE

The post-marketing data includes isolated cases of overdose in which the reported highest daily dose of entacapone has been 16,000 mg. The acute symptoms and signs in these cases of overdose included confusion, decreased activity, somnolence, hypotonia, skin discolouration and urticaria.

Management of acute overdose is symptomatic.

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

## PRESENTATION AND STORAGE CONDITIONS

Comtan 200 mg tablet: oval, brownish-orange, unscored, film-coated tablet embossed with "Comtan" on one side; packs of 30, 60, 100 or 300 tablets.

Not all pack sizes marketed.

Store below 25ºC.

Keep out of the reach of children.

## NAME AND ADDRESS OF THE SPONSOR

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

® = Registered Trademark

## POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4).

## DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 19 December 2003

Date of most recent amendment: 04 September 2013

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(com040913i.doc) based on CDS dated 18 June 2013