NOVARTIS

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו בפברואר 2014

COMTAN®

(entacapone)

200 mg film-coated tablets

Prescribing Information

1 Name of the medicinal product

COMTAN®

2 Qualitative and quantitative composition

Tablet containing 200 mg entacapone.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Film-coated tablet.

Brownish-orange, oval, biconvex film-coated tablet with Comtan® engraved on one side.

4 Clinical particulars

4.1 Therapeutic indications

Entacapone is indicated as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilized on those combinations.

4.2 Posology and method of administration

Entacapone should only be used in combination with levodopa/benserazide or levodopa/carbidopa. The prescribing information for these levodopa preparations is applicable to their concomitant use with entacapone.

Posology

One 200 mg tablet is taken with each levodopa/dopa decarboxylase inhibitor dose. The maximum recommended dose is 200 mg ten times daily, i.e. 2,000 mg of entacapone.

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 days to first weeks after initiating entacapone treatment. 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, according to the clinical condition of the patient.

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

If entacapone 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.

Renal impairment does not affect the pharmacokinetics of entacapone and there is no need for dose adjustment. However, for patients who are receiving dialysis therapy, a longer dosing interval may be considered (see section 5.2 Pharmacokinetic properties).

Hepatic impairment: see section 4.3 Contraindications.

Elderly

No dosage adjustment of entacapone is required for elderly patients.

Children

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

Method of administration

Entacapone is administered orally and simultaneously with each levodopa/carbidopa or levodopa/benserazide dose.

Entacapone can be taken with or without food (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Hepatic impairment.

Patients with pheochromocytoma due to the increased risk of hypertensive crisis.

A previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

Concomitant use of entacapone and non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).

Concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and entacapone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Known hypersensitivity to entacapone or to any of the excipients.

4.4 Special warnings and precautions for use

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 characterized by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g. agitation, confusion, coma),

hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase (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 entacapone and other dopaminergic medications. When considered necessary, withdrawal of entacapone and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

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

Because of its mechanism of action, entacapone may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with medicinal products metabolized by catechol-O-methyl transferase (COMT), e.g. rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Entacapone is always given as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for entacapone treatment. Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5 to 10% more than from standard levodopa/carbidopa preparations. Consequently, undesirable dopaminergic effects may be more frequent when entacapone is added to levodopa/benserazide treatment (see section 4.8 Undesirable effects). To reduce levodopa-related dopaminergic adverse reactions, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating entacapone treatment, according to the clinical condition of the patient (see section 4.2 Posology and method of administration and 4.8 Undesirable effects).

Entacapone may aggravate levodopa-induced orthostatic hypotension. Entacapone should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

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

Entacapone used in combination with levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson’s disease and caution should therefore be exercised when driving or operating machines (see section 4.7 Effects on ability to drive and use machines).

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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of entacapone with carbidopa has been observed with the recommended treatment schedule. Pharmacokinetic interaction with benserazide has not been studied.

In single-dose studies in healthy volunteers, no interactions were observed between entacapone and imipramine or between entacapone and moclobemide. Similarly, no interactions between entacapone and selegiline were observed in repeated-dose studies in parkinsonian patients. However, the experience of the clinical use of entacapone with several drugs, including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine, and 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. Caution should be exercised when these medicinal products are used concomitantly with entacapone (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Entacapone may be used with selegiline (a selective MAO-B inhibitor), but the daily dose of selegiline should not exceed 10 mg.

Entacapone may form chelates with iron in the gastrointestinal tract. Entacapone and iron preparations should be taken at least 2 to 3 hours apart (see section 4.8 Undesirable effects).

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. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products.

Due to its affinity to cytochrome P450 2C9 *in vitro* (see section 5.2 Pharmacokinetic properties), entacapone 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% [CI_{90} 11 to 26%]. The INR values increased on average by 13% [CI_{90} 6 to 19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

4.6 Pregnancy and breast-feeding

Pregnancy

No overt teratogenic or primary fetotoxic effects were observed in animal studies in which the exposure levels of entacapone were markedly higher than the therapeutic exposure levels. As there is no experience in pregnant women, entacapone should not be used during pregnancy.

Breast-feeding

In animal studies entacapone was excreted in milk. The safety of entacapone in infants is unknown. Women should not breast-feed during treatment with entacapone.

4.7 Effects on ability to drive and use machines

Comtan 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 section 4.4 Special warnings and precautions for use).

Entacapone may, together with levodopa, cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

4.8 Undesirable effects

Very common undesirable effects found in double-blind placebo controlled phase III studies are dyskinesia, nausea, and abnormal urine (see below).

Common undesirable effects found in double-blind placebo controlled phase III studies are diarrhoea, Parkinsonism aggravated, dizziness, abdominal pain, insomnia, dry mouth, fatigue, hallucinations, constipation, dystonia, increased sweating, hyperkinesia, headache, leg cramps, confusion, paroniria, fall, postural hypotension, vertigo and tremor.

Most of the undesirable effects 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 effects. The other major class of undesirable effects are gastrointestinal symptoms, including e.g. nausea, vomiting, abdominal pains, constipation and diarrhoea. Urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.

Usually undesirable effects caused by entacapone are mild to moderate. The most common undesirable effects leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea, 2.5%) and dopaminergic symptoms (e.g. dyskinesias, 1.7%).

Dyskinesias (27%), nausea (11%), diarrhoea (8%), abdominal pain (7%) and dry mouth (4.2%) were reported significantly more often with entacapone than with placebo in clinical studies.

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

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 treatment (6 months) with entacapone a clinically significant decrease in haemoglobin has been observed in 1.5% of patients.

Rare reports of clinically significant increases in liver enzymes have been received.

The following adverse drug reactions, listed below in Table 1, have been accumulated both from clinical studies with entacapone and since the introduction of entacapone into the market.

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data, since no valid estimate can be derived from clinical trials or epidemiological studies).

Psychiatric disorders	
Common	Insomnia, hallucinations, confusion, nightmares
Very rare	Agitation
Nervous system disorders	
Very common	Dyskinesia
Common	Parkinsonism aggravated, dizziness, dystonia, hyperkinesia
Cardiac disorders	
Common	Ischaemic heart disease events other than myocardial infarction*(e.g. angina pectoris)
Uncommon	Myocardial infarction*
Gastrointestinal disorders	
Very common	Nausea
Common	Diarrhoea, abdominal pain, dry mouth, constipation, vomiting
Very rare	Anorexia, colitis
Hepato-biliary disorders	
Rare	Hepatic function tests abnormal
Not known	Hepatitis with mainly cholestatic features
Skin and subcutaneous tissue disorders	
Rare	Erythematous or maculopapular rash
Very rare	Urticaria
Not known	Skin, hair, beard and nail discolourations
Renal and urinary disorders	
Very common	Urine discolouration
General disorders and administration site conditions	
Common	Fatigue, sweating increased, fall
Very rare	Weight decrease

* The incidence rates of myocardial infarction and other ischaemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2082 patients with end-of-dose motor fluctuations receiving entacapone.

Entacapone used in combination with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes (see section 4.7 Effects on ability to drive and use machines).

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

Isolated cases of rhabdomyolysis have been reported.

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 section 4.4 Special warnings and precautions for use).

4.9 Overdose

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 overdosing is symptomatic.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: catechol-O-methyl transferase inhibitor, ATC code: N04BX02.

Entacapone belongs to a new therapeutic class, 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 COMT enzyme. This leads to an increase in the bioavailability of levodopa and an increased amount of levodopa available to the brain. Entacapone thus prolongs the clinical response to levodopa.

Entacapone inhibits the COMT enzyme mainly in peripheral tissues. COMT inhibition in red blood cells closely follows the plasma concentrations of entacapone, thus clearly indicating the reversible nature of COMT inhibition.

Clinical studies

In two phase III double-blind studies in altogether 376 patients with Parkinson's disease and end-of-dose motor fluctuations, entacapone or placebo was given with each levodopa/dopa decarboxylase inhibitor dose. The results are given in Table 2. In study I, daily ON time (hours) was measured from home diaries and in study II, the proportion of daily ON time was measured.

Table 2:

Daily ON time (Mean ± SD)

Study I: Daily ON time (h)			
	Entacapone(n=85)	**Placebo(n=86)**	**Difference**
Baseline	9.3±2.2	9.2±2.5	
Week 8-24	10.7±2.2	9.4±2.6	1h 20 min (8.3%) $CI_{95\%}$ 45 min, 1 h 56
Study II: Proportion of daily ON time (%)			
	Entacapone(n=103)	**Placebo(n=102)**	**Difference**
Baseline	60.0±15.2	60.8±14.0	
Week 8-24	66.8±14.5	62.8±16.80	4.5% (0 h 35 min) $CI_{95\%}$ 0.93%, 7.97%

There were corresponding decreases in OFF time.

In study 1 OFF-time was reduced by 24% compared with 0% in the placebo group.

In study 2 OFF-time was reduced by 18% compared with 5% in the placebo group.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance

Absorption

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

The peak concentration (C_{max}) in plasma is usually reached about one hour after a 200 mg entacapone tablet. 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.

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. Approximately 92% of the dose is eliminated during beta-phase, with a short elimination half-life of 30 minutes. The total clearance of entacapone is about 800 mL/min.

Entacapone is extensively bound to plasma proteins, mainly to albumin. In human plasma the unbound fraction is about 2.0% in the therapeutic concentration range. At therapeutic concentrations, entacapone does not displace other extensively bound drugs (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these drugs at therapeutic or higher concentrations.

Metabolism

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%.

Data from in vitro studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 microM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Elimination

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

b) Characteristics in patients

The pharmacokinetic properties of entacapone are similar in both young and elderly adults. The metabolism of the medicinal product 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 section 4.3 Contraindications). Renal impairment does not affect the pharmacokinetics of entacapone. However, a longer dosing interval may be considered for patients who are receiving dialysis therapy.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, and carcinogenic potential. In repeated-dose toxicity studies, anaemia most likely due to iron chelating properties of entacapone was observed. In studies of reproduction toxicity, decreased fetal weight and a slightly delayed bone development were noticed in rabbits at systemic exposure levels in the therapeutic range.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core: microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate.

Film-coating: hypromellose cellulose 6cPs, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red iron oxide, titanium dioxide.
Each tablet contains 1.82 mg sucrose and approximately 5.6 mg sodium.

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Do not store above 30°C. After first opening the bottle, the medicine may be used for up to 12 months. Pay particular attention to close the bottle immediately after each use.

Comtan must be kept out of the reach and sight of children.

6.5 Nature and content of container

Amber glass bottles (hydrolytic class III) with white tamper-resistant polypropylene closures containing 30 tablets.

6.6 Instructions for use and handling

No special requirements.

Manufacturer:

Orion Corporation, Espoo, Finland

For: Novartis Pharma AG, Basel, Switzerland

Registration Holder:

Novartis Israel Ltd., 36 Shacham St., Petach-Tikva.