Scheduling status

S4

Proprietary name (and dosage form)

COMTAN® 200 mg tablets

Composition

Each film-coated tablet contains 200 mg entacapone as active ingredient.

List of excipients:

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

Film-coating: hypromellose, polysorbate 80, glycerol 85 %, sucrose, magnesium stearate, yellow iron oxide (E172), titanium dioxide (E171).

Pharmacological classification

A.5.4.1 Anti-parkinsonism preparations

Pharmacological action Pharmacodynamics

Entacapone belongs to a therapeutic class, the Catechol-0-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.

Pharmacokinetics 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 gastro-intestinal 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 B-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 agents (e.g. warfarin, salicylic acid, phenylbutazone and diazepam), nor is it displaced to any significant extent by any of these agents 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 AUG 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 (ICSO ~ 4 microM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (see Interactions)

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 % has been formed through oxidation.

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 insufficiency (Child-Pugh Class A and B), which leads to an increased plasma concentration of entacapone both in the absorption and elimination phases (see Contra-indications).

Renal insufficiency does not affect the pharmacokinetics of entacapone. However, a longer dosing interval may be considered for patients who are receiving dialysis therapy.

Indications

COMTAN 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 stabilised on those combinations.

Contra-indications

Hypersensitivity to COMTAN or to any of the excipients of the medicinal product.

Liver impairment.

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

Concomitant use of COMTAN 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 COMTAN (see Interactions).

A previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.

Warnings

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 COMTAN treatment.

NMS, including rhabdomyolysis and hyperthermia, is characterized by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g. agitation, contusion, 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.

Because of its mechanism of action, COMTAN may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action. Thus, COMTAN should be administered cautiously to patients being treated with medicinal products metabolised by COMT, e.g. rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine (see Interactions).

COMTAN is always given as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for COMTAN treatment. COMTAN 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 (see Side-effects). To reduce levodopa-related dopaminergic adverse effects, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating COMTAN treatment, according to the clinical condition of the patient (see Dosage and Directions for use and Side-effects).

COMTAN may aggravate levodopa-induced orthostatic hypotension. COMTAN 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 COMTAN 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 COMTAN treatment is initiated.

Isolated cases of hepatitis with cholestatic features have been reported.

COMTAN 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.

For patients experiencing diarrhoea, monitoring of weight is recommended in order to avoid potential excessive weight decrease.

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.

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.

Pathological gambling, increased libido and hypersexuality have been reported in Parkinson's disease patients treated with COMTAN in association with levodopa.

Interaction with other medicinal products and other forms of interaction

No interaction of COMTAN 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

COMTAN and imipramine, or between COMTAN and moclobemide.

Similarly, no interactions were observed between COMTAN and selegiline in repeated-dose studies in parkinsonian patients. However, experience of the clinical use of COMTAN with several drugs, including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine, and medicinal products that are metabolised 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 COMTAN (see Contra-indications and Warnings).

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

COMTAN may form chelates with iron in the gastrointestinal tract. COMTAN and iron preparations should be taken at least 2-3 hours apart (see Side-effects).

COMTAN 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 Pharmacokinetics), COMTAN may potentially interfere with drugs whose metabolism is dependent on this isoenzyme, such as S-warfarin. However, in an interaction study in healthy volunteers, COMTAN 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 INR values increased on average by 13% [CI_{90} 6-19 %]. Thus, more frequent monitoring of INR is recommended when COMTAN treatment is initiated for patients receiving warfarin

Pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Lactation

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

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. COMTAN® 200 mg may, together with levodopa cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using 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.

Dosage and directions for use

COMTAN 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 COMTAN.

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

COMTAN can be taken with or without food (see Pharmacokinetics).

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 g of entacapone.

COMTAN enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reaction, 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 according to the clinical condition of the patient.

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

Renal insufficiency does not affect the pharmacokinetics of COMTAN and there is no need for dose adjustment. However, for patients who are receiving dialysis therapy, a longer dosing interval may be considered (see Pharmacokinetics).

Elderly

No dosage adjustment of COMTAN 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.

Side-effects and special precautions

Most of the undesirable effects caused by COMTAN relate to the increased dopaminergic activity and occur most commonly at the beginning of the treatment. Reduction of levodopa dosage may decrease the severity and frequency of these events.

Usually undesirable effects caused by COMTAN are mild to moderate. The most common undesirable effects leading to discontinuation of COMTAN 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 COMTAN 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 (1,4 to 2 g per day) than with the lower doses of **COMTAN.**

The following adverse drug reactions, listed below in Table 1, have been effects found in double-blind placebo-controlled phase III studies.

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); rare including isolated cases (≥1/10,000, <1/1,000); not known (cannot be estimated from the available data, since no valid estimate can be derived from clinical studies or epidemiological studies).

Table 1	
Psychiatric disorders	
Common	Insomnia, hallucinations, confusion, paroniria
Nervous system disorders	
Very common	Dyskinesia
Common	Parkinsonism aggravated, dizziness, dystonia, hyperkinesia, headache, tremor,
Ear and labyrinth disorders	
Common	Vertigo
Musculoskeletal, connective tissue and bone disorders	
Common	Leg cramps
Gastrointestinal disorders	
Very common	Nausea
Common	Diarrhoea, abdominal pain, mouth dry, constipation, vomiting
Very rare	Anorexia
Hepato-blllary disorders	
Rare	Hepatic function tests abnormal

Vascular disorders	
Common	Postural hypotension
Renal and urinary disorders	
Very common	Urine discolouration
General disorders and administration site conditions	
Common	Fatigue, sweating increased, fall

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

The following adverse drug reactions, listed below in Table 2, have been accumulated since the introduction of COMTAN into the market.

Table 2
Psychiatric disorders
Agitation
Gastrointestinal disorders
Anorexia, colitis
Hepato-biliary disorders
Hepatitis mainly with cholestatic features.

Skin and subcutaneous tissue disorders Erythematous or maculopapular rash, urticaria, skin, hair, beard and nail discolouration.
General disorders and administration site conditions Weight decrease

COMTAN used in combination with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes (see Warnings).

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

Isolated cases of rhabdomyolysis have been reported.

Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as COMTAIN in association with levodopa, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. *(See 'Warnings")*

Known symptoms of overdosage and particulars of its treatment

The post-marketing data includes isolated cases of overdose in which the reported highest daily dose of COMTAN 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.

Identification

Brownish-orange, oval shaped, film-coated tablet with 'COMTAN' printed on it.

Presentation

Packs of 30, 60, 100 or 500 tablets in amber glass bottles.

Storage instructions

Store below 25 °C.

KEEP OUT OF THE REACH OF CHILDREN

Registration number

32/5.4.1/0684

Name and business address of the registration certificate holder

NOVARTIS SOUTH AFRICA (Pty) Ltd

72 Steel Road Spartan Kempton Park

1619

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