AUSTRALIAN PRODUCT INFORMATION – TRIDOPA (LEVODOPA/ CARBIDOPA/ ENTACAPONE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Levodopa, carbidopa and entacapone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIDOPA tablets come in six strengths each containing a 4:1 ratio of levodopa to carbidopa anhydrous combined with entacapone 200 mg in an immediate release formulation. Containing levodopa, carbidopa anhydrous, entacapone, the strengths are 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg and 200/50/200 mg.

For the full list of excipients, see *section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

TRIDOPA 50/12.5/200: Levodopa/Carbidopa/Entacapone 50 mg/12.5 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '50' on one side and 'LEC' on the other side.

TRIDOPA 75/18.75/200: Levodopa/Carbidopa/Entacapone 75 mg/18.75 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '75' on one side and 'LEC' on the other side.

TRIDOPA 100/25/200: Levodopa/Carbidopa/Entacapone 100 mg/25 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '100' on one side and 'LEC' on the other side.

TRIDOPA 125/31.25/200: Levodopa/Carbidopa/Entacapone 125 mg/31.25 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '125' on one side and 'LEC' on the other side.

TRIDOPA 150/37.5/200: Levodopa/Carbidopa/Entacapone 150 mg/37.5 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '150' on one side and 'LEC' on the other side.

TRIDOPA 200/50/200: Levodopa/Carbidopa/Entacapone 200 mg/50 mg/200 mg film-coated tablet; Red, oval, biconvex coated tablet with '200' on one side and 'LEC' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRIDOPA is indicated for the management of patients with Parkinson's disease who are experiencing motor fluctuations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Each TRIDOPA tablet is to be taken orally either with or without food (see *section 5.2 Pharmacokinetic properties*). One tablet contains one treatment dose and the tablet may only be administered as whole tablets.

The optimum daily dosage of TRIDOPA must be determined by careful titration in each patient. The daily dose should preferably be optimised using one of the six available tablet strengths

(50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg, or 200/50/200 mg levodopa/carbidopa/entacapone).

Patients should be instructed to take only one TRIDOPA tablet per dose administration. The experience with total daily dosage greater than 200 mg carbidopa is limited, whereas patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting. The maximum recommended daily dose of entacapone is 2000 mg, therefore the maximum levodopa/carbidopa/entacapone dose must not exceed 10 tablets per day, for the levodopa/carbidopa/entacapone strengths of 50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, and 150/37.5/200 mg. Ten (10) tablets of TRIDOPA 150/37.5/200 mg equals 375 mg of carbidopa a day.

Therefore, using a maximum recommended daily dose of 375 mg of carbidopa, the maximum daily dose of TRIDOPA 200/50/200 mg is 7 tablets per day.

The maximum total daily levodopa dose administered in the form of TRIDOPA should not exceed 1500 mg.

Generally speaking, TRIDOPA is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone.

How to transfer patients taking levodopa/ DDC inhibitor (carbidopa or benserazide) preparations and entacapone tablets to levodopa/carbidopa/entacapone

a. Patients who are currently treated with entacapone and with standard release levodopa/carbidopa in doses equal to TRIDOPA tablet strengths can be directly transferred to corresponding TRIDOPA tablets. For example, a patient taking one tablet of 100/25 mg of levodopa/carbidopa with one tablet of entacapone 200 mg four times daily can take one 100/25/200 mg TRIDOPA tablet four times daily in place of their usual levodopa/carbidopa and entacapone doses.

b. When initiating TRIDOPA therapy for patients currently treated with entacapone and levodopa/carbidopa in doses not equal to one of the available levodopa/carbidopa/entacapone tablet strengths, TRIDOPA dosing should be carefully titrated for optimal clinical response. At the initiation, TRIDOPA should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.

c. When initiating TRIDOPA in patients currently treated with entacapone and levodopa/benserazide in a standard release formulation, discontinue dosing of levodopa/benserazide the previous night and start TRIDOPA the next morning. Begin with a dosage of levodopa/carbidopa/entacapone that will provide either the same amount of levodopa or slightly (5-10 %) more.

How to transfer patients taking levodopa/DDC inhibitor preparations not currently taking entacapone to TRIDOPA

Initiation of TRIDOPA may be considered at corresponding doses to current treatment in some patients with Parkinson's disease and end-of-dose motor fluctuations, who are not stabilized on their current standard release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to TRIDOPA is not recommended for patients who have dyskinesias and whose daily levodopa dose is above 800 mg (see Table 1). In such patients it is

advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to levodopa/carbidopa/entacapone.

Table 1: The percentage of Parkinson's disease patients decreasing levodopa dose by 4 6 weeks after entacapone initiation as grouped by baseline levodopa dose and presence of dyskinesias (data from NOMECOMT, SEESAW, CELOMEN and UK IRISH trials)

	Levodopa dose < 600 mg/day (n=180)	**Levodopa dose 600-800 mg/day (n=180)**	**Levodopa dose > 800 mg/day (n=180)**
Patients without dyskinesias	4%	21%	28%
Patients with dyskinesias	31%	43%	66%

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dosage by 10-30% within the first days to first weeks after initiating TRIDOPA treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

There are no data on transferring patients from controlled-release formulations of levodopa/carbidopa to TRIDOPA.

Dosage adjustment during the course of the treatment

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of TRIDOPA should be considered, within the dosage recommendations described in the above section. When less levodopa is required, the total daily dosage of TRIDOPA should be reduced either by decreasing the frequency of administration, by extending the time between doses, or by decreasing the strength of TRIDOPA at administration. If other levodopa products are used concomitantly with a TRIDOPA tablet, the maximum dosage recommendations should be followed.

Discontinuation of TRIDOPA therapy

If TRIDOPA treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is transferred to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see *section 4.4 Special warnings and precautions for use – Neuroleptic Malignant Syndrome and Rhabdomyolysis*).

Children and adolescents

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

Elderly patients

No dosage adjustment of TRIDOPA is required for elderly patients (see *section 5.2 Pharmacokinetic properties – pharmacokinetics in the elderly*).

Hepatic impairment

It is advised that TRIDOPA should be administered cautiously to patients with mild to moderate hepatic impairment. Dose reduction may be needed (see *section 5.2 Pharmacokinetic properties – Pharmacokinetics in patients with liver impairment*).

Renal impairment

Renal insufficiency does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, therefore TRIDOPA therapy should be administered cautiously to patients with severe renal impairments including those receiving dialysis therapy (see *section 5.2 Pharmacokinetic properties – Pharmacokinetics in patients with renal impairment*).

4.3 CONTRAINDICATIONS

TRIDOPA is contraindicated in the following:

- Known hypersensitivity to the active substances or to any of the excipients
- Pregnancy and breast feeding (see *section 4.6 Fertility, pregnancy and lactation*).
- Severe liver impairment (see *section 5.2 Pharmacokinetic properties – Pharmacokinetics in patients with liver impairment*).
- Patients with narrow-angle glaucoma.
- Patients with phaeochromocytoma due to the increased risk of hypertensive crisis.
- Concomitant use of TRIDOPA 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 TRIDOPA is contraindicated.
- A previous history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis (see *section 4.4 Special warnings and precautions for use – Neuroleptic Malignant Syndrome and Rhabdomyolysis*).
- Because levodopa may activate malignant melanoma, TRIDOPA should not be used in patients with suspicious undiagnosed skin lesions or a history of malignant melanoma.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Precautions relating to levodopa component of TRIDOPA

TRIDOPA is not recommended for the treatment of drug-induced extrapyramidal reactions.

TRIDOPA should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.

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

All patients treated with levodopa should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current psychosis should be treated with caution.

Concomitant administration of antipsychotic drugs with dopamine receptor-blocking properties particular D_2 receptor antagonists should be carried out with caution and the patient carefully observed for loss of antiparkinsonian effect or worsening of antiparkinsonian symptoms.

Patients with chronic wide-angle glaucoma may be treated with levodopa/carbidopa/entacapone with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure.

TRIDOPA may induce orthostatic hypotension. Therefore, it should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

Entacapone in association 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).*

Neuroleptic Malignant Syndrome and Rhabdomyolysis

Neuroleptic Malignant Syndrome (NMS), including rhabdomyolysis and hyperthermia, is characterised 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. In individual cases, only some of these symptoms and/or findings may be evident. Early diagnosis is important for the appropriate management of NMS.

A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatinine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone (see *section 4.2 Dose and method of administration – Discontinuation of therapy*). Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment. When considered necessary, withdrawal of TRIDOPA and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of TRIDOPA, an increase in levodopa dosage may be necessary.

Prescribers should exercise caution when switching patients from TRIDOPA to levodopa/DDC inhibitor therapy without entacapone. When considered necessary, the replacement of levodopa/carbidopa/entacapone with levodopa and DDC inhibitor without entacapone should proceed slowly and an increase in levodopa dosage may be necessary.

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 levodopa/carbidopa/entacapone may be a sign of colitis. In the event of prolonged or persistent diarrhoea, the drug 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.

Dopamine dysregulation syndrome (DDS)

Dopamine dysregulation syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see *section 4.8 Adverse effects (Undesirable effects)*).

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, medication use and punding (repetitive purposeless activity) can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including TRIDOPA. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences. Review of treatment is recommended if such symptoms develop.

Hallucinations

Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials of entacapone, hallucinations developed in approximately 4.0% of patients treated with 200 mg entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg entacapone and placebo, respectively. Hallucinations led to hospitalisation in 1.0% and 0.3% of patients in the 200 mg entacapone and placebo groups, respectively.

Dyskinesia

Entacapone may potentiate the dopaminergic side effects of levodopa and may therefore cause and/or exacerbate pre-existing 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 were 1.5% and 0.8% for 200 mg entacapone and placebo, respectively.

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other non-ergot derived drugs (e.g. entacapone, levodopa) 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 7-17 months.

General anaesthesia

If general anaesthesia is required, therapy with TRIDOPA may be continued for as long as the patient is permitted to take fluids and medication by mouth. If therapy has to be stopped temporarily, TRIDOPA may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Patient monitoring

As with levodopa, periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with levodopa/carbidopa/entacapone.

Concurrent Diseases

TRIDOPA should be administered cautiously to patients with biliary obstruction, hepatic disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease.

Use in combination with other antiparkinsonian medications

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 patients who received placebo in combination with any of these medications. The doses of other antiparkinsonian medications may require adjustment when TRIDOPA is being substituted in patients not currently taking entacapone.

Use in hepatic impairment

Refer to *section 4.2 Dose and method of administration – Hepatic impairment* and *section 5.2 Pharmacokinetic properties – Pharmacokinetics in patients with liver impairment*.

Use in renal impairment

Refer to *section 4.2 Dose and method of administration – Renal impairment* and *section 5.2 Pharmacokinetic properties – Pharmacokinetics in patients with renal impairment*

Use in the elderly

Refer to *section 4.2 Dose and method of administration – Elderly patients* and *section 5.2 Pharmacokinetic properties – Pharmacokinetics in the elderly*.

Paediatric use

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

Effects on laboratory tests

Refer to *section 4.8 Adverse effects (Undesirable effects) – Adverse effects in laboratory tests*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with TRIDOPA therapy.

Antihypertensive drugs

Symptomatic postural hypotension may occur when levodopa is added to the treatment of patients already receiving antihypertensive drugs. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants and levodopa/carbidopa (see *section 4.2 Dose and method of administration*). No interactions were observed between entacapone and imipramine and between entacapone and moclobemide in single dose studies in healthy volunteers.

MAO inhibitors

For patients receiving nonselective MAO inhibitors see *section 4.3 Contraindications*.

Selegiline

No interactions were observed between entacapone and selegiline in repeated dose studies in patients with Parkinson's disease. Entacapone may be used in combination with selegiline (a selective MAO-B inhibitor), but the daily dose should not exceed 10 mg.

Warfarin

Due to entacapone's affinity to cytochrome P450 2C9 *in vitro* (see *section 5.2 Pharmacokinetic properties – metabolism and excretion*), levodopa/carbidopa/entacapone may potentially interfere with drugs whose metabolism is dependent on this isoenzyme, such as S-warfarin. However, in an interaction study with 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 TRIDOPA is initiated for patients receiving warfarin.

Dopamine D_2 receptor antagonists

Dopamine D_2 receptor antagonists (e.g. Phenothiazines, butyrophenones, risperidone and isoniazid) may reduce the therapeutic effects of levodopa.

Phenytoin and papaverine

Phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these drugs with TRIDOPA should be carefully observed for loss of therapeutic response.

Metoclopramide

Although metoclopramide may increase the bioavailability of levodopa by increasing the gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Pyroxidine

TRIDOPA can be given to patients receiving supplemental pyroxidine. Oral coadministration of 10-25 mg of pyroxidine hydrochloride (vitamin B6) with levodopa may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyroxidine; therefore, TRIDOPA can be given to patients receiving supplemental pyroxidine.

Drugs metabolised by COMT

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 (epinephrine), noradrenaline (norepinephrine), dopamine, dobutamine, alpha-methyldopa, and apomorphine, paroxetine). Patients should be carefully monitored if entacapone is administered in combination with any of these drugs.

When a single 400 mg dose of entacapone was given together with intravenous isoprenaline and adrenaline (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 adrenaline (epinephrine) respectively. Therefore, drugs known to be metabolised by COMT, such as isoprenaline, adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, dobutamine, methyldopa and apomorphine 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.

Food

Levodopa competes with certain amino acids, and so its absorption from levodopa/carbidopa/entacapone maybe impaired in some patients on a high protein diet.

Other forms of interactions

Levodopa and entacapone may form chelates with iron in the gastrointestinal tract. Therefore, TRIDOPA and iron preparations should be taken at least 2-3 hours apart (see *section 4.8 Adverse effects (Undesirable effects)*).

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.

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).

Trehalose

TRIDOPA tablets contain trehalose dihydrate. Patients with rare problems of *trehalose* insufficiency (primary or secondary) should not take TRIDOPA tablets.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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.

Use in pregnancy – Pregnancy Category B3[1]

There are no adequate data from the use of combination levodopa/carbidopa/entacapone in pregnant women. In rats and rabbits, co-administration of levodopa, carbidopa and entacapone during the period of organogenesis at oral doses of less than (levodopa, carbidopa) and twice (entacapone) the intakes on a mg/m^2 basis at the recommended human dose of levodopa/carbidopa/entacapone, was not teratogenic. Levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. 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, foetotoxicity 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 entacapone in pregnant women. Hence, the use of levodopa/carbidopa/entacapone during pregnancy is contraindicated.

Use in lactation

In animal studies, carbidopa and entacapone were excreted in milk. Oral administration of entacapone to rats from early pregnancy to weaning reduced offspring bodyweight at maternal exposure (plasma AUC) of 26 times the maximal clinical exposure, but not at an exposure of six times the maximal clinical exposure. It is not known whether levodopa, carbidopa, or entacapone is excreted in human milk. Therefore, levodopa/carbidopa/entacapone is contraindicated for nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TRIDOPA may cause 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.

TRIDOPA may have a major influence on the ability to drive and use machines. Patients being treated with levodopa/carbidopa/entacapone 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

[1] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.
Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

machines) until such recurrent episodes have resolved (see *section 4.4 Special warnings and precautions for use*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

TRIDOPA combines levodopa/carbidopa and entacapone in one product. The following section describes the undesirable effects reported for levodopa/carbidopa and for entacapone used in combination with levodopa/DDC inhibitor.

Levodopa/carbidopa

Adverse effects that occur frequently with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction.

More common reactions

The most common adverse effects are dyskinesias including choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs to consider levodopa dosage reduction. Nausea is also related to enhanced central dopaminergic activity, is a common adverse effect of levodopa/carbidopa.

Other adverse effects associated with levodopa/carbidopa therapy are mental changes, including paranoid ideation and psychotic episodes; depression, with or without development of suicidal tendencies; cognitive dysfunction; and dopamine dysregulation syndrome. Adding entacapone to levodopa/DDC inhibitor therapy (carbidopa or benserazide), e.g. initiation of levodopa/carbidopa/entacapone treatment in an entacapone naive patient may affect the occurrence of some of these mental changes (see Table 2 - Psychiatric disorders).

Less common reactions

Less frequent adverse effects of levodopa/carbidopa therapy are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence.

Gastrointestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, chest pain, dyspnoea and paraesthesia have occurred rarely with levodopa/carbidopa.

Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa therapy has not been established.

Dopamine dysregulation syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/carbidopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see *section 4.4 Special warnings and precautions for use*).

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 containing levodopa including TRIDOPA (see *section 4.4 special warnings and precautions for use – Impulse control disorders*).

Other adverse effects that have been reported with levodopa and may, therefore, be potential adverse effects of levodopa/carbidopa/entacapone as well, include:

Neurological: Ataxia, numbness, increased hand tremor, muscle twitching, muscle cramp, trismus, activation of latent Horner's syndrome, falling, gait abnormalities.

Psychiatric events**:** Confusion, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.

Gastrointestinal**:** Dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain, constipation, diarrhoea, flatulence, burning sensation of the tongue.

Metabolic**:** Weight gain or loss, oedema.

Skin and subcutaneous tissue**:** Flushing, increased sweating, dark sweat, rash, hair loss.

Genitourinary**:** Urinary retention, urinary incontinence, dark urine, priapism.

Eye**:** Diplopia, blurred vision, dilated pupils, oculogyric crises.

Miscellaneous**:** Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome (see *section 4.3 Contraindications*), malignant melanoma.

Entacapone

The most frequent adverse reactions caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of the treatment. Reduction of levodopa dosage usually decreases the severity and frequency of the reactions. The other major class of adverse reactions are gastrointestinal symptoms, including nausea, vomiting, abdominal pain, constipation and diarrhoea. Urine may be discoloured reddish-brown by entacapone but this is a harmless phenomenon.

Usually the adverse reactions caused by entacapone in combination with levodopa/DDC inhibitor are mild to moderate. In clinical studies the most common adverse reactions leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea) and increased dopaminergic adverse reactions of levodopa (e.g. dyskinesias).

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

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.

Dyskinesias, nausea, diarrhoea, abdominal pain and dry mouth were reported significantly more often with entacapone than with placebo (Table 2), based on pooled data from clinical studies involving 603 patients taking levodopa/DDC inhibitor and entacapone and 400 patients taking levodopa/DDC inhibitor therapy and placebo. 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.

Table 2. Adverse reactions 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 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

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

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.

Adverse reactions from post-marketing reports

The following are additional adverse drug reactions that have been reported since the introduction of entacapone for combination use with levodopa/DDC inhibitor. 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

Very rare: hepatitis with cholestatic features

Psychiatric disorders

Very rare: agitation

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.

Isolated cases of angiodema have been reported after initiation of levodopa/carbidopa/ entacapone.

Other

The following adverse reactions have also been observed:

Gastrointestinal disorders

Common: dyspepsia

Musculoskeletal and connective tissue disorders

Very common: muscle, musculoskeletal and connective tissue pain

Common: arthralgia

Renal and urinary disorders

Common: urinary tract infection

Adverse effects in laboratory tests

The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and entacapone.

Abnormalities include elevated values of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. Commonly, levels of blood urea nitrogen and uric acid are lower during administration of levodopa/carbidopa than with levodopa alone. Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported. Positive Coombs' tests have been reported, both for levodopa/carbidopa and for levodopa alone, but haemolytic anaemia is extremely rare.

Levodopa/carbidopa may cause false positive results when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glycosuria.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at *www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The post-marketing data includes isolated cases of overdose in which the reported highest daily doses of levodopa and entacapone have been at least 10,000 mg and 40,000 mg, respectively. The acute symptoms and signs in these cases of overdose included agitation, confusional state, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration, discolourations of skin, tongue and conjunctiva, and chromaturia. Management of acute overdosage with levodopa/carbidopa/entacapone therapy is similar to acute overdosage with levodopa. Pyridoxine, however, is not effective in reversing the actions of levodopa/carbidopa/entacapone tablets. Hospitalisation is advised and general supportive measures should be employed with repeated doses of activated charcoal over time. This may hasten the elimination of entacapone in particular by decreasing its absorption/reabsorption from the GI tract. The adequacy of the

respiratory, circulatory and renal systems should be carefully monitored and appropriate supportive measures employed. Intravenous fluids should be administered judiciously and an adequate airway maintained. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmia. If required, appropriate, anti-arrhythmic therapy should be given. The possibility that the patient has taken other drugs in addition to TRIDOPA should be taken into consideration. The value of dialysis in the treatment of overdosage is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The symptoms of Parkinson's disease are thought to be related to depletion of dopamine in the corpus striatum. Dopamine does not cross the blood-brain barrier. Levodopa, the precursor of dopamine, crosses the blood brain barrier and relieves the symptoms of the disease. As levodopa is extensively metabolised in the periphery only a small portion of a given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors. Carbidopa and benserazide are peripheral dopa decarboxylase (DDC) inhibitors which reduce the peripheral metabolism of levodopa to dopamine and, thus, more levodopa is available to the brain. When decarboxylation of levodopa is reduced with the co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse effects such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, COMT becomes the major peripheral metabolic pathway catalysing the conversion of levodopa to 3-O-methyldopa (3-OMD), a potentially harmful metabolite of levodopa. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased area under the curve (AUC) in the pharmacokinetic profile of levodopa. Consequently, the clinical response to each dose of levodopa is enhanced and prolonged. The reversibility of COMT inhibition with entacapone has been demonstrated in bioassays of COMT activity in red blood cells; red blood cell COMT inhibition tightly correlates with plasma concentrations of the drug.

Clinical trials

Each levodopa/carbidopa/entacapone tablet, provided in six single-dose strengths, contains carbidopa and levodopa in a 1:4 ratio and a 200 mg dose of entacapone. Four strengths 50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg and 200/50/ 200 mg have been shown to be bioequivalent to the corresponding doses of standard-release levodopa/carbidopa 100/25 mg tablets and entacapone 200 mg tablets. Hence, the results from previous trials of entacapone 200 mg administered concomitantly with standard levodopa/carbidopa preparations are applicable to the effects of levodopa/carbidopa/entacapone, as well.

The anticipated therapeutic effects of levodopa/carbidopa/entacapone are based on the results of two pivotal Phase III studies in 376 Parkinson's disease patients with end-of-dose motor fluctuations receiving entacapone or placebo with each levodopa/DDC inhibitor dose.

The 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 entacapone 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 entacapone 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, entacapone 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 entacapone 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 entacapone 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 entacapone 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone. Both levodopa and entacapone are rapidly absorbed and eliminated. Carbidopa is absorbed and eliminated slightly slower compared with levodopa. When given separately without the two other active ingredients, the bioavailability for levodopa is 15 - 33 %, for carbidopa 40 -70 % and for entacapone 29 - 36 % (35 % after a 200 mg oral dose). High protein meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone. The effect of food on the tablets has not been evaluated.

Levodopa

The pharmacokinetic characteristics of levodopa following the administration of single-dose levodopa/carbidopa/entacapone tablets are summarised in Table 3.

Table 3. Pharmacokinetic characteristics of levodopa with different tablet strengths of levodopa/carbidopa/entacapone in healthy elderly subjects (mean ±SD)

Tablet strength*	$AUC_{0-\infty}$(ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
50/12.5/200 mg	1044 ± 314	473 ± 154	1.1 ± 0.5
100/25/200 mg	2906 ± 715	975 ± 247	1.4 ± 0.6

150/37.5/200 mg	3774 ± 118	1272 ± 329	1.5 ± 0.9
*levodopa/carbidopa/entacapone			

Levodopa is bound to plasma protein only to a minor extent of about 10-30 %.

Carbidopa

Following administration of the levodopa/carbidopa/entacapone tablets as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5 to 3.4 hours on average. The mean C_{max} ranged from about 40 to 125 ng/mL and the mean AUC from 170 to 700 ng.h/mL, with different tablet strengths providing 12.5 mg, 25 mg or 37.5 mg of carbidopa. Carbidopa is bound approximately 36 % bound to plasma protein.

Entacapone

Following administration of the levodopa/carbidopa/entacapone tablets as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0 to 1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/mL and the AUC 1250 to 1450 ng.h/mL after administration of different levodopa/carbidopa/entacapone tablet strengths all providing 200 mg entacapone. Entacapone is extensively bound to plasma proteins (about 98 %), mainly to serum albumin. The distribution volumes of both levodopa (0.36 - 1.6 L/kg) and entacapone (0.27 L/kg) are moderately small while no data for carbidopa are available.

Metabolism and Excretion

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 ($IC_{50} \sim 4$ μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (see *section 4.5 Interactions with other medicines and other forms of interactions*)

Levodopa

The elimination-half life ($t_{½el}$) is 0.6 - 1.3 hours for levodopa. Levodopa is extensively metabolised to various metabolites, decarboxylation by dopa decarboxylase (DDC) and *O*-methylation by catechol-*O*-methyltransferase (COMT) being the most important pathways.

Carbidopa

The elimination-half life ($t_{½el}$) is 2 -3 hours for carbidopa. Carbidopa is metabolised to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid) which are excreted in the urine as glucuronides and unconjugated compounds. Unchanged carbidopa accounts for 30 % of the total urinary excretion.

Entacapone

The elimination-half life is ($t_{½el}$) 0.4 - 0.7 hours for entacapone. Entacapone is almost completely metabolised prior to excretion; only about 0.2 % is excreted unchanged in urine. The main metabolic pathway is glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5 % of the total amount in plasma. Ten percent of an entacapone dose is excreted in urine, and 90 % in faeces by biliary excretion. Of entacapone metabolites found in

urine only about 1 % have been formed through oxidation. Total plasma clearance for levodopa is in the range of 0.55 - 1.38 L/kg/h and for entacapone is in the range of 0.70 L/kg/h.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

Pharmacokinetics in patients with liver impairment

Levodopa/Carbidopa/Entacapone should be administered cautiously to patients with biliary obstruction or hepatic disease. There are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment, but biliary excretion appears to be the major route of excretion of entacapone.

Entacapone

Hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200 mg entacapone was administered alone. A single 200 mg dose of entacapone, without levodopa/DDI inhibitor co-administration, 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, levodopa/carbidopa/entacapone should be administered with care to patients with biliary obstruction or hepatic disease.

Pharmacokinetics in patients with renal impairment

Levodopa/Carbidopa/Entacapone should be administered cautiously to patients with severe renal disease (see *section 4.2 Dose and method of administration*). There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. However, a longer dosing interval of levodopa/carbidopa/entacapone may be considered for patients who are receiving dialysis therapy.

Entacapone

No important effects of renal function on the pharmacokinetics of entacapone were found. The pharmacokinetics of entacapone have been investigated after a single 200 mg entacapone dose, without levodopa-dopa decarboxylase inhibitor co-administration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12 mL/sec/1.73 m^2), moderate impairment (n=10; creatinine clearance ranging from 0.60 - 0.89 mL/sec/1.73 m^2), and severe impairment (n=7; creatinine clearance ranging from 0.20 - 0.44 mL/sec/1.73 m^2).

Pharmacokinetics in the elderly

Levodopa/Carbidopa/Entacapone tablets have not been studied in Parkinson's disease patients or in healthy volunteers older than 75 years old. In the pharmacokinetics studies conducted in healthy volunteers following single dose of carbidopa/levodopa/entacapone (as levodopa/carbidopa/entacapone or as separate carbidopa/levodopa and entacapone tablets):

Levodopa

The AUC of levodopa is significantly (on average 10 - 20%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of levodopa between younger (45–60 years) and elderly subjects (60–75 years).

Carbidopa

There is no significant difference in the C_{max} and AUC of carbidopa, between younger (45 – 60 years) and elderly subjects (60–75 years).

Entacapone

The AUC of entacapone is significantly (on average, 15%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of entacapone between younger (45-60 years) and elderly subjects (60-75 years).

Gender differences in pharmacokinetics

The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and/or entacapone. In the pharmacokinetic studies with levodopa/carbidopa/ entacapone, the bioavailability of levodopa is higher in women than in men, primarily due to the difference in body weight, while there is no gender difference with carbidopa and entacapone. Following a single dose of carbidopa, levodopa and entacapone together, either as levodopa/carbidopa/entacapone or as separate carbidopa/levodopa and entacapone tablets in healthy volunteers (age range 45-74 years):

Levodopa

The plasma exposure (AUC & C_{max}) of levodopa is significantly higher in females than males (on average, 40% for AUC and 30% for C_{max}). These differences are primarily explained by body weight. Other published literature showed significant gender effect (higher concentrations in females) even after correction for body weight.

Carbidopa

There is no gender difference in the pharmacokinetics of carbidopa.

Entacapone

There is no gender difference in the pharmacokinetics of entacapone.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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. Entacapone was negative in an *in vivo* assay for clastogenicity and assays for DNA damage. Carbidopa was positive in bacterial and mammalian gene mutation assays, but negative in an *in vivo* assay for clastogenicity. A combination of levodopa, carbidopa and entacapone was negative in a bacterial gene mutation assay and two *in vivo* assays for clastogenicity.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain croscarmellose sodium, hyprolose, trehalose dihydrate, powdered cellulose, sodium sulfate, microcrystalline cellulose, magnesium stearate and OPADRY II complete film coating system 85G35208 RED (ARTG 108033).

The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

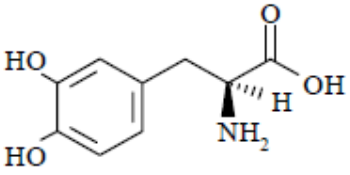
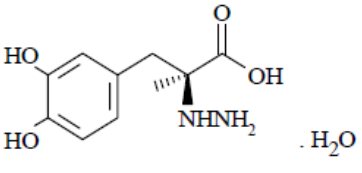
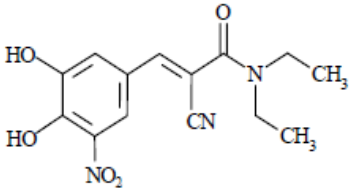
Bottles (consisting of HDPE container with PP closure) of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Levodopa	**Carbidopa**	**Entacapone**
		

CAS number

Levodopa	**Carbidopa**	**Entacapone**
59-92-7	38821-49-7	130929-57-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINES - S4

8 SPONSOR

Stada Pharmaceuticals Australia Pty Ltd
Level 3, Suite 204, 26 Rodborough Road
Frenchs Forest NSW 2086
Telephone: 1800 791 660
Email: *medinfo@stada.com.au*
Website: *https://www.stada.com.au/*

9 DATE OF FIRST APPROVAL

4 October 2013

10 DATE OF REVISION

15 June 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4 & 4.8	Add warning for Dopamine dysregulation syndrome (DDS)
4.4 & 4.8	Revise warning for Impulse control disorders
4.6	Amend warning that TRIDOPA is contraindicated during pregnancy and lactation.
4.8	Add 'Other' AEs.
6.1	Updated the AAN.