**CELTOR TABLETS**
**(LEVODOPA, CARBIDOPA AND ENTACAPONE TABLETS 50mg + 12.5mg + 200mg/ 100mg + 25mg + 200mg)**

## BRAND OR PRODUCT NAME
CELTOR TABLETS 50+12.5+200mg/100+25+200 mg

## NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)
CELTOR TABLETS 50+12.5+200 MG
Each film-coated tablet contains:
Levodopa USP ..... 50mg
Carbidopa USP ..... 12.5mg
Entacapone USP ..... 200mg

CELTOR TABLETS 100+25+200 MG
Each film-coated tablet contains:
Levodopa USP ..... 100mg
Carbidopa USP .....25mg
Entacapone USP ..... 200mg

## PRODUCT DESCRIPTION
CELTOR TABLETS 50+12.5+200 MG
Light brown to grayish red colored, round, biconvex, film coated tablets with debossed "50" on one side and plain on other side.

CELTOR TABLETS 100+25+200 MG
Light brown to grayish red colored, oval shaped, film coated tablets with debossed "100" on one side and plain on other side.

## DOSAGE FORM
Film coated bilayered tablet

## PHARMACODYNAMICS
According to the current understanding, the symptoms of Parkinson's disease are 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 reactions such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, catechol-O-methyltransferase (COMT) becomes the major peripheral metabolic pathway catalyzing 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.

## PHARMACOKINETICS

### General characteristics of the active substances

**Absorption/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 substances, the bioavailability for levodopa is 15-33%, for carbidopa 40-70% and for entacapone 35% after a 200 mg oral dose. 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 distribution volume of both levodopa (Vd 0.36-1.6 l/kg) and entacapone ($Vd_{ss}$ 0.27 l/kg) is moderately small while no data for carbidopa are available.

Levodopa is bound to plasma protein only to a minor extent of about 10-30% and carbidopa is bound approximately 36%, while entacapone is extensively bound to plasma proteins (about 98%), mainly to serum albumin. At therapeutic concentrations, entacapone does not displace other extensively bound active substances (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these substances at therapeutic or higher concentrations.

**Metabolism and elimination**
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 is metabolized to two main metabolites which are excreted in the urine as glucuronides and unconjugated compounds. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone is almost completely metabolized prior to excretion via urine (10 to 20%) and bile/faeces (80 to 90%). The main metabolic pathway is glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5% of plasma total amount.

Total 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. The elimination-half life is ($t_{1/2}$) is 0.6-1.3 hours for levodopa, 2-3 hours for carbidopa and 0.4-0.7 hours for entacapone, each given separately.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs on repeated administration.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 µM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19).

**Characteristics in patients**

**Elderly**

In elderly patients given without carbidopa and entacapone, the absorption of levodopa is greater and elimination is slower in elderly than in young subjects. However, after combination of carbidopa with levodopa, the absorption of levodopa is similar between the elderly and the young, but the AUC is still 1.5 fold greater in the elderly due to decreased DDC activity and lower clearance by aging. There are no significant differences in the AUC of carbidopa or entacapone between younger (45–64 years) and elderly subjects (65–75 years).

**Gender**

Bioavailability of levodopa is significantly higher in women than in men. In the pharmacokinetic studies with FDC levodopa, carbidopa and 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.

**Hepatic impairment**

The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases. No particular studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment are reported, however, it is advised that FDC levodopa, carbidopa and entacapone should be administered cautiously to patients with mild or moderate hepatic impairment.

**Renal impairment**

Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. However, a longer dosing interval of FDC levodopa, carbidopa and entacapone may be considered for patients who are receiving dialysis therapy.

**INDICATIONS**

Celtor (carbidopa, levodopa and entacapone) is indicated to treat patients with idiopathic Parkinson's disease:

1) To substitute (with equivalent strength of each of the 3 components) for immediate release of carbidopa/levodopa and entacapone previously administered as individual products.
2) To replace immediate release of carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" (only for patients taking a total daily dose of levodopa of 600 mg or less and not experiencing dyskinesias (see Dosage & Administration).

**DOSAGE AND ADMINISTRATION**

The optimum daily dose must be determined by careful titration of levodopa in each patient.

Patients should be instructed to take only one tablet per dose administration. Patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting. While the experience with total daily dose greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2,000 mg and therefore the maximum dose is 10 tablets per day for the strengths of 50 mg/12.5 mg/200 mg, and 100 mg/25 mg/200 mg.

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

**Starting Celtor therapy**

**Switching from levodopa/DDC inhibitor (carbidopa or benserazide) preparation and entacapone to Celtor.**

Usually Celtor is intended for use in patients already receiving treatment with corresponding doses of standard release levodopa/DDC inhibitor and entacapone.

As with levodopa/carabdopa, non-selective monoamine oxidase (MAO) inhibitor are contraindicated for use with Celtor. These inhibitors must be disconlinued at least two weeks prior to initiating therapy with Celtor . Celtor may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCI).

*a.* Patients who are currently treated with entacapone and with standard release levodopa/carbidopa in doses equal to Celtor tablet strengths can be directly transferred to corresponding Celtor tablets. For example:

| Levodopa/Carbidopa | Entacapone | Equivalent Celtor |
|---|---|---|
| 50/12.5 mg | 200 mg | 50/12.5/200 mg |
| 100/25 mg | 200 mg | 100/25/200 mg |

*b.* When initiating Celtor therapy for patients currently treated with entacapone and levodopa/carbidopa in doses not equal to Celtor 100 mg/25 mg/200 mg or 50 mg/12.5 mg/200 mg tablets, Celtor dosing should be carefully titrated for optimal

clinical response. At the initiation, Celtor should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.

*c.* When initiating Celtor in patients currently treated with entacapone and levodopa/benserazide in a standard release formulation, the dosing of levodopa/benserazide should be discontinued for one night, and Celtor should be started in the next morning. The therapy should begin with a dosage of celtor that will provide either the same amount of levodopa or slightly (5-10%) more.

**Switching patient not currently treated with entacapone to Celtor**
As with levodopa/carabdopa, non-selective monoamine oxidase (MAO) inhibitor are contraindicated for use with Celtor. These inhibitors must be disconlinued at least two weeks prior to initiating therapy with Celtor . Celtor may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCI).

Initiation of Celtor 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 stabilised on their current standard release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Celtor is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate treatment (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Celtor.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dose by 10-30% within the first days to first weeks after initiating Celtor 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.

**Dose 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 Celtor should be considered, within the dose recommendations.

When less levodopa is required, the total daily dose of Celtor should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Celtor at an administration.

If other levodopa products are used concomitantly with a Celtor tablet, the maximum dose recommendations should be followed.

**Discontinuation of Celtor therapy**
If Celtor treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is switched 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, rhabdomyolysis).

**Children and Adolescents**
The safety and efficacy of Celtor in children aged below 18 years have not been established. No data are available.

**Elderly**
No dose adjustment of Celtor is required for elderly patients.

**Hepatic impairment**
Caution is recommended when administering Celtor to patients with mild to moderate hepatic impairment. Dose reduction may be necessary (See section PHARMACOKINETICS).

**Renal insufficiency**
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 Celtor therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapy (See section PHARMACOKINETICS).

**Method of Administration**
Each tablet is to be taken orally either with or without food (See section PHARMACOKINETICS). One tablet contains one treatment dose and the tablet may only be administered as whole tablets.

**CONTRAINDICATIONS**
- Known hypersensitivity to the active substances or to any of the excipients.
- Severe hepatic impairment.
- Narrow-angle glaucoma.
- Pheochromocytoma.
- Coadministration of non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).
- Coadministration of a selective MAO-A inhibitor and a selective MAO-B inhibitor {see section INTERACTIONS, other antiparkinsonian medicinal products). These inhibitors must be discontinued at least two weeks prior to initiating therapy with Celtor.
- A history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

FDC of levodopa, carbidopa and entacapone is not recommended for the treatment of drug-induced extrapyramidal reactions

FDC of levodopa, carbidopa and entacapone therapy should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease, history of peptic ulcer disease or history 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 FDC of levodopa, carbidopa and entacapone 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 antipsychotics with dopamine receptor-blocking properties, particularly $D_2$ receptor antagonists should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms.

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

FDC of levodopa, carbidopa and entacapone may induce orthostatic hypotension. Therefore, FDC of levodopa, carbidopa and entacapone should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

Levodopa has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson’s diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Celtor. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

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 also section EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

The doses of other antiparkinsonian medicinal products may need to be adjusted when FDC of levodopa, carbidopa and entacapone treatment is substituted for a patient currently not treated with entacapone.

Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has been reported rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment. NMS, including rhabdomyolysis and hyperthermia, is characterised by motor symptoms (rigidity, myoclonus, tremor), 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. The 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 creatine 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.

When considered necessary, withdrawal of Celtor and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of Celtor, an increase in levodopa dosage may be necessary.

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

If general anaesthesia is required, therapy with FDC of levodopa, carbidopa and entacapone may be continued for as long as the patient is permitted to take fluids and medicinal products by mouth. If therapy has to be stopped temporarily, FDC of levodopa, carbidopa and entacapone may be restarted as soon as oral medicinal products can be taken at the same daily dose as before.

Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with FDC of levodopa, carbidopa and entacapone.

For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhoea appearing during use of 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.

Levodopa/carbidopa may cause false positive result 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.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
Celtor may have major influence on the ability to drive and use machines.

Patients being treated with Celtor 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 also section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Levodopa, carbidopa and entacapone together may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

**INTERACTIONS**
To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian medicinal products with FDC of levodopa, carbidopa and entacapone therapy. Entacapone in high doses may affect the absorption of carbidopa. However, no interaction with carbidopa has been reported with the recommended treatment schedule (200 mg of entacapone up to 10 times daily). Interactions between entacapone and selegiline have been investigated in repeated dose studies in Parkinson's disease patients treated with levodopa/DDC inhibitor and no interaction was reported. When used with FDC of levodopa, carbidopa and entacapone, the daily dose of selegiline should not exceed 10 mg.

Because Celtor contains entacapone, it should not be used concurrently with entacapone.

Caution should be exercised when the following active substances are administered concomitantly with levodopa therapy.

**Antihypertensives**
Symptomatic postural hypotension may occur when levodopa is initiated in patients already receiving antihypertensives. 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. Interactions between entacapone and imipramine and between entacapone and moclobemide have been investigated in single dose studies in healthy volunteers. No pharmacodynamic interactions were reported. A significant number of Parkinson's disease patients have been treated with the combination of levodopa, carbidopa and entacapone with several active substances 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, paroxetine). No pharmacodynamic interactions have been reported. However, caution should be exercised when these medicinal products are used concomitantly with FDC of levodopa, carbidopa and entacapone (see also section CONTRAINDICATIONS and section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

**Other active substances**
Dopamine receptor antagonists (e.g. some antipsychotics and antiemetics), phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these medicinal products with FDC of levodopa, carbidopa and entacapone should be carefully observed for loss of therapeutic response.

Due to entacapone's affinity to cytochrome P450 2C9 *in vitro*, FDC of levodopa, carbidopa and entacapone may potentially interfere with active substances whose metabolism is dependent on this isoenzyme, such as S-warfarin.

**Other forms of interactions**
Since levodopa competes with certain amino acids, the absorption of FDC of levodopa, carbidopa and entacapone may be impaired in some patients on high protein diet.

Levodopa and entacapone may form chelates with iron in the gastrointestinal tract. Therefore, Celtor and iron preparations should be taken at least 2-3 hours apart (See section UNDESIRABLE EFFECTS).

**In vitro data**
Entacapone binds to human albumin binding site II which also binds several other medicinal products, including diazepam and ibuprofen. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products. Accordingly, to date there has been no indication of such interactions.

**PREGNANCY AND LACTATION**
Pregnancy
There are no adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicity of the separate compounds. The potential risk for humans is unknown. FDC of levodopa, carbidopa and entacapone should not be used during pregnancy.

Breastfeeding
Levodopa is excreted in human breast milk. There is evidence that breastfeeding is suppressed during treatment with levodopa. Carbidopa and entacapone were excreted in milk in animals but is not known whether they are excreted in human breast milk. The safety of levodopa, carbidopa or entacapone in the infant is not known. Women should not breast-feed during treatment with FDC of levodopa, carbidopa and entacapone.

Fertility
No adverse reactions on fertility were reported in preclinical studies with entacapone, carbidopa or levodopa alone. Fertility studies in animals have not been conducted with the combination of entacapone, levodopa and carbidopa.

## ADVERSE EFFECTS / UNDESIRABLE EFFECTS

### a. Summary of the safety profile

The most frequently reported adverse reactions with FDC of levodopa, carbidopa and entacapone are dyskinesias; gastrointestinal symptoms including nausea and diarrhoea, respectively; muscle, musculoskeletal and connective tissue pain and harmless reddish-brown discolouration of urine (chromaturia). Serious events of gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been reported with FDC of levodopa, carbidopa and entacapone or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur with FDC of levodopa, carbidopa and entacapone.

### b. Tabulated list of adverse reactions

**Table 1.** Adverse reactions

| | |
|---|---|
| **Blood and lymphatic system disorders** | |
| Common: | Anaemia |
| Uncommon: | Thrombocytopenia |
| **Metabolism and nutrition disorders** | |
| Common: | Weight decreased*, decreased appetite* |
| **Psychiatric disorders** | |
| Common: | Depression, hallucination, confusional state*, abnormal dreams*, anxiety, insomnia |
| Uncommon: | Psychosis, agitation* |
| Not known: | Suicidal behaviour |
| **Nervous system disorders** | |
| Very common: | Dyskinesia* |
| Common: | Parkinsonism aggravated (e.g. bradykinesia)*, tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness*, headache |
| Not known: | Neuroleptic malignant syndrome* |

| | |
|---|---|
| **Eye disorders** | |
| Common: | Blurred vision |
| **Cardiac disorders** | |
| Common: | Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris)* , irregular heart rhythm |
| Uncommon: | Myocardial infarction* |
| **Vascular disorders:** | |
| Common: | Orthostatic hypotension, hypertension |
| Uncommon: | Gastrointestinal haemorrhage |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea |
| **Gastrointestinal disorders** | |
| Very common: | Diarrhoea*, nausea* |
| Common: | Constipation*, vomiting*, dyspepsia, abdominal pain and discomfort*, dry mouth* |
| Uncommon: | Colitis*, dysphagia |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatic function test abnormal* |
| Not known: | Hepatitis with mainly cholestatic features* |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Rash*, hyperhidrosis |
| Uncommon: | Discolourations other than urine (e.g. skin, nail, hair, sweat)* |
| Rare: | Angioedema |
| Not known: | Urticaria* |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Muscle, musculoskeletal and connective tissue pain* |
| Common: | Muscle spasms, arthralgia |

| | |
|---|---|
| Not known: | Rhabdomyolysis* |
| **Renal and urinary disorders** | |
| Very common: | Chromaturia* |
| Common: | Urinary tract infection |
| Uncommon: | Urinary retention |
| **General disorders and administration site conditions** | |
| Common: | Chest pain, peripheral oedema, fall, gait disturbance, asthenia, fatigue |
| Uncommon: | Malaise |

*Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone. See section c.

**c. Description of selected adverse reactions**
Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk in Table 1. Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat.

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

Parkinson's disease patient treated with dopamine agonists and other dopaminergic treatments such as Celtor, especially at high doses, have been reported as exhibiting signs of Pathological gambling, increased libido, hypersexuality and other urges, generally reversible upon reduction of the dose or treatment discontinuation. Entacapone in association with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes.

Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

**Overdose and Treatment**
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 overdose with FDC of levodopa, carbidopa and entacapone therapy is similar to acute overdose with levodopa. Hospitalisation is advised and general supportive measures should be employed with immediate gastric lavage and repeated doses of 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. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmias. If required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient has taken other active substances in addition to FDC of levodopa, carbidopa and entacapone should be taken into consideration. The value of dialysis in the treatment of overdose is not known.

**STORAGE CONDITIONS**

Store below 30$^{o}$C, Protect from light and moisture.

**PACKAGING AVAILABLE**

Celtor tablets are packed in Alu-Alu blister of 10 tablets. Such blister strips containing 10 tablets are packed in boxes of 10’s & 30’s along with product information leaflet.

**DATE OF REVISION OF PACKAGE INSERT**
22.02.2018

**NAME AND ADDRESS OF MANUFACTURER**


**TORRENT PHARMACEUTICALS LTD.**
Indrad 382 721, District: Mehsana
INDIA.