เอกสารกำกับยาภาษาอังกฤษ

Entacapone Teva
(Entacapone 200 mg film coated tablet)

1. NAME OF THE MEDICINAL PRODUCT
Entacapone Teva 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 200 mg entacapone.
Excipient with known effect
Each film-coated tablet contains 0.74 mg soya lecithin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Light brown, biconvex, ellipse-shaped film-coated tablets with approximately 18 mm length and 10 mm width, embossed 'E200' on one side, plain on the other side.

4. CLINICAL PARTICULARS

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

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

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

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

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

Entacapone 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 entacapone is initiated.

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

Patients with hepatic impairment
See section 4.3.

Elderly patients
No dosage adjustment of entacapone is required for elderly patients.
Paediatric population
The safety and efficacy of Entacapone Teva in children below age 18 have not been established. No data are available.

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

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

4.3 Contraindications
- Hypersensitivity to the active substance or to peanut or soya or to any of the excipients listed in section 6.1.
- Hepatic impairment.
- Phaeochromocytoma.
- Concomitant use of entacapone and non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).
- Concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and entacapone (see section 4.5).
- A previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

4.4 Special warnings and precautions for use
Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has been observed rarely in patients with Parkinson's disease.

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.

Neither NMS nor rhabdomyolysis have been reported in association with entacapone treatment from controlled trials in which entacapone was discontinued abruptly. Since the introduction into the market, isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone and other concomitant dopaminergic medicinal products. When considered necessary, withdrawal of entacapone and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

Entacapone therapy should be administered cautiously to patients with ischemic heart disease.

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

Entacapone is always given as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for entacapone treatment. Entacapone increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5-10% more than

from standard levodopa/carbidopa preparations. Consequently, adverse dopaminergic reactions may be more frequent when entacapone is added to levodopa/benserazide treatment (see also section 4.8).
To reduce levodopa-related dopaminergic adverse reactions, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating entacapone treatment, according to the clinical condition of the patient (see sections 4.2 and 4.8).
Entacapone may aggravate levodopa-induced orthostatic hypotension. Entacapone should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

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

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 4.7).

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 medicinal product should be discontinued and appropriate medical therapy and investigations considered.

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

Entacapone Teva contains soya lecithin. Patients who are hypersensitive to peanut or soya, should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction of entacapone with carbidopa has been observed with the recommended treatment schedule. Pharmacokinetic interaction with benserazide has not been studied.

In single-dose studies in healthy volunteers, no interactions were observed between entacapone and imipramine or between entacapone and moclobemide. Similarly, no interactions between entacapone and selegiline were observed in repeated-dose studies in parkinsonian patients. However, the experience of the clinical use of entacapone with several medicinal products, 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, alphamethyldopa, apomorphine, and paroxetine) is still limited. Caution should be exercised when these medicinal products are used concomitantly with entacapone (see also sections 4.3 and 4.4).

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

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

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

Due to its affinity to cytochrome P450 2C9 *in vitro* (see section 5.2), entacapone may potentially interfere with medicinal products with metabolism 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 INR values increased on average by 13% [CI_{90} 6–19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines
Entacapone Teva in association with levodopa may have major influence on the ability to drive and use machines. Entacapone may, together with levodopa, cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

Patients being treated with entacapone in association with levodopa and presenting with somnolence and/or sudden sleep onset episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes have resolved (see also section 4.4).

4.8 Undesirable effects

Summary of the safety profile
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 decreases the severity and frequency of these 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 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, 2.5%) and increased dopaminergic adverse reactions of levodopa (e.g. dyskinesias, 1.7%).

Dyskinesias (27%), nausea (11%), diarrhoea (8%), abdominal pain (7%) and dry mouth (4.2%) were reported significantly more often with entacapone than with placebo in pooled data from clinical studies involving 406 patients taking the medicinal product and 296 patients taking placebo.

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

Tabulated list of adverse reactions

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

Table 1. Adverse drug reactions*

Psychiatric disorders	Common: Very rare:	Insomnia, hallucinations, confusion, paroniria Agitation
Nervous system disorders	Very common: Common:	Dyskinesia Parkinsonism aggravated, dizziness, dystonia, hyperkinesia
Cardiac disorders**	Common: Uncommon:	Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris) Myocardial infarction
Gastrointestinal disorders	Very common: Common: Very rare: Not known:	Nausea Diarrhoea, abdominal pain, dry mouth, constipation, vomiting Anorexia Colitis
Hepatobiliary disorders	Rare: Not known:	Hepatic function tests abnormal Hepatitis with mainly cholestatic features (see section 4.4.)
Skin and subcutaneous tissue disorders	Rare: Very rare: Not known:	Erythematous or maculopapular rash Urticaria Skin, hair, beard and nail discolorations
Renal and urinary disorders	Very common:	Urine discoloration
General disorders and administration site conditions	Common: Very rare	Fatigue, sweating increased, fall Weight decrease

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

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

Description of selected adverse reactions

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

Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Entacapone Teva in association with levodopa (see section 4.4).

Isolated cases of NMS have been reported following abrupt reduction or discontinuation of entacapone and other dopaminergic treatments.

Isolated cases of rhabdomyolysis have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other dopaminergic agents, ATC code: N04BX02.

Entacapone belongs to a new therapeutic class, catechol-O-methyl transferase (COMT) inhibitors. It is a reversible, specific, and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa preparations. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the COMT enzyme. This leads to a higher levodopa AUC. The amount of levodopa available to the brain is increased. Entacapone thus prolongs the clinical response to levodopa.

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

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

Table 2. Daily ON time (Mean ±SD)

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

There were corresponding decreases in OFF time.

The % change from baseline in OFF time was -24% in the entacapone group and 0% in the placebo group in study I. The corresponding figures in study II were –18% and –5%.

5.2 Pharmacokinetic properties
General characteristics of the active substance
Absorption
There are large intra- and interindividual variations in the absorption of entacapone.

The peak concentration (C_{max}) in plasma is usually reached about one hour after ingestion of a 200 mg entacapone tablet. The substance is subject to extensive first-pass metabolism. The bioavailability of entacapone is about 35% after an oral dose. Food does not affect the absorption of entacapone to any significant extent.

Distribution
After absorption from the gastrointestinal tract, entacapone is rapidly distributed to the peripheral tissues with a distribution volume of 20 litres at steady state (Vd_{ss}). Approximately 92% of the dose is eliminated during ß-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 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.

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

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC_{50} ~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).

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

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 in both the absorption and elimination phases (see section 4.3). Renal impairment does not affect the pharmacokinetics of entacapone. However, a longer dosing interval may be considered for patients who are receiving dialysis therapy.

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

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core
Cellulose, microcrystalline
Povidone
Starch, pregelatinised

Magnesium stearate

Film-coating
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Macrogol
Iron oxide yellow (E172)
Lecithin (soya)
Iron oxide red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
HDPE tablet containers with polypropylene screw caps with desiccant insert containing 100 film-coated tablets.

7. MARKETING AUTHORISATION HOLDER
Teva Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

MANUFACTURER
TEVA Gyógyszergyár Zrt.
Debrecen, Hungary

8. MARKETING AUTHORISATION NUMBER(S)
[To be completed]

9. DATE OF AUTHORISATION
[To be completed]

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