

1. NAME OF THE MEDICINAL PRODUCT

Entacapone Medochemie film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg entacapone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Brown capsule shaped, convex film-coated tablet.

4. CLINICAL PARTICULARS

a. Therapeutic indications

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

b. 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.

Renal impairment

Renal impairment does not affect the pharmacokinetics of entacapone and there is no need for dose

adjustment. However, for patients who are receiving dialysis therapy, a longer dosing interval may be considered (see section 5.2).

Hepatic impairment

See section 4.3.

Elderly

No dosage adjustment of entacapone is required for elderly patients.

Paediatric population

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

Method of administration

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

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

c. Contraindications

- Hypersensitivity to the active substance 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.

d. 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 ischaemic heart disease. Because of its mechanism of action, entacapone may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with medicinal products metabolised by catechol-O-methyl transferase (COMT), e.g. rimexetone, 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, undesirable dopaminergic effects, e.g. dyskinesia, were more common in patients who received entacapone and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to those who received placebo with this combination. The doses of other antiparkinsonian 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 Medochemie 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.

e. 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: rimeterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine, and paroxetine) is still limited. Caution should be exercised when these medicinal products are used concomitantly with entacapone (see 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 anti-

inflammatory 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 in healthy volunteers, entacapone did not change the plasma levels of S-warfarin, while the AUC for R-warfarin increased on average by 18% [CI90 11–26%]. The INR values increased on average by 13% [CI90 6–19%]. Thus, control of INR is recommended when entacapone treatment is initiated for patients receiving warfarin.

f. 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.

g. Effects on ability to drive and use machines

Entacapone Medochemie in association with levodopa may have a 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).

h. 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 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:	Ischaemic 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 discolourations
Renal and urinary disorders Very common:	Urine discolouration
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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 ischaemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2,082 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 Medochemie 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

i. 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

a. 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-of-dose motor fluctuations, entacapone or placebo was given with each levodopa/dopa decarboxylase inhibitor dose. The results are given in Table 2. In study I, daily ON time (hours) was measured from home diaries and in study II, the proportion of daily ON time.

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%) CI95% 45 min, 1 h 56
Study II: Proportion of daily On time (%)			
	Entacapone (n=103)	Placebo (n=102)	Difference
Baseline	60.0±15.2	60.8±14.0	
Week 8-24	66.8±14.5	62.8±16.80	4.5% (0 h 35 min) CI95% 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%.

b. 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 (V_{dss}). Approximately 92% of the dose is eliminated during β -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 ($IC_{50} \sim 4 \mu M$). 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 people and older people. 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.

c. 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

a. List of excipients

Tablet core: cellulose microcrystalline 102, mannitol E421, sodium starch glycolate type A, magnesium stearate E572.

Film-coating: hypromellose 5mPa•s E464, titanium dioxide E171, talc E553b, macrogol 400, macrogol 6000, Iron oxide yellow (E172), Iron oxide red (E172), Iron oxide black (E172)

b. Incompatibilities

Not applicable.

c. Shelf life

The expiry date is indicated on the package materials.

d. Special precautions for storage

Store below 25°C.

e. Nature and contents of container

Blister opaque PVC/PVDC/Aluminium containing 30, 60, 100 or 500 tablets.

Not all pack sizes may be marketed.

f. Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Devries & CO. LTD 32, HaBarzel st., 69710 Tel Aviv

8. MANUFACTURER

Medochemie Ltd., 1-10 Constantinoupoleos Street, 3011, Limassol, Cyprus.

9. MARKETING AUTHORISATION NUMBER

160-98-35150

10. DATE OF REVISION OF THE TEXT

November 2020