SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENCAPIA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ENCAPIA contains 200mg entacapone.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.
Brown, capsule-shaped, convex, film- coated tablets with dimension 19×10 mm.

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 motor fluctuations, 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.

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.

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.

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).

Hepatic impairment: see section 4.3.

Elderly: No dosage adjustment of entacapone is required for elderly patients.

Pediatric population: The safety and efficacy of entacapone 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 any of the excipients.
- 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. 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.

Isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone and other dopaminergic medications. 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-O-methyl 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, 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 drug should be discontinued and appropriate medical therapy and investigations considered.

Impulse control disorders

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 ENCAPIA 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.

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, 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 section 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 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

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.

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 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

Very common undesirable effects found in doubleblind placebo controlled phase III studies are dyskinesia, nausea, and abnormal urine (see below). Common undesirable effects found in double-blind placebo controlled phase III studies are diarrhoea, Parkinsonism aggravated, dizziness, abdominal pain, insomnia, dry

mouth, fatigue, hallucinations, constipation, dystonia, increased sweating, hyperkinesia, headache, leg cramps, confusion, paroniria, fall, postural hypotension, vertigo and tremor.

Most of the undesirable effects caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of treatment. Reduction of levodopa dosage may decrease the severity and frequency of these effects. The other major class of undesirable effects are gastrointestinal symptoms, including e.g. nausea, vomiting, abdominal pains, constipation and diarrhoea. Urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.

Usually undesirable effects caused by entacapone are mild to moderate. The most common undesirable effects leading to discontinuation of entacapone treatment have been gastrointestinal symptoms (e.g. diarrhoea, 2.5%) and dopaminergic symptoms (e.g. dyskinesias, 1.7%).

Dyskinesias (27%), nausea (11%), diarrhoea (8%), abdominal pain (7%) and dry mouth (4.2%) were reported significantly more often with entacapone than with placebo in clinical studies.

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

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 treatment (6 months) with entacapone a clinically significant decrease in haemoglobin has been observed in 1.5% of patients.

Rare reports of clinically significant increases in liver enzymes have been received.

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

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <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).

Table 1

Psychiatric disorders	
Common	Insomnia, hallucinations, confusion, nightmares
Very rare	Agitation
Nervous system disorders	
Very common	Dyskinesia
Common	Parkinsonism aggravated, dizziness, dystonia, hyperkinesia
Cardiac disorders	
Common	Ischaemic heart disease events other than myocardial infarction* (e.g. angina pectoris)
Uncommon	Myocardial infarction*
Gastrointestinal disorders	
Very common	Nausea

Common	Diarrhoea, abdominal pain, dry mouth, constipation, vomiting
Very rare	Anorexia, colitis
Hepato-biliary disorders	
Rare	Hepatic function tests abnormal
Not known	Hepatitis with mainly cholestatic features
Skin and bcutaneo us tissue disorders	
Rare	Erythematous or maculopapular rash
Very rare	Urticaria
Not known	Skin, hair, beard and nail discolourations
Renal and urinary disorders	
Very common	Urine discolouration
General disorders and administration site conditions	
Common	Fatigue, sweating increased, fall
Very rare	Weight decrease

* 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 2082 patients with end-of-dose motor fluctuations receiving entacapone.

Entacapone used in combination with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes (see also section 4.7).
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. 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 in association with levodopa (see also section 4.4).

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-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%) $CI_{95\%}$ 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.

Metabolism

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

Core:

Cellulose microcrystalline 102

Mannitol E421

Sodium Starch Glycolate -Type A

Magnesium Stearate. E572

Coating:

Hypromellose 2910 5mPa•s E464

Titanium dioxide E171

Macrogol 400

Iron oxide yellow E172

Iron oxide red E172

Iron oxide black E172

Talc E553b

Macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Brown amber glass bottles (hydrolytic class III) with white LDPE closures: Store below 30°C in the original package.

6.5 Nature and contents of container

The tablets are packed in:

- Brown amber glass bottles (hydrolytic class III) containing 30 or 60 tablets, with white LDPE closures and with one white cylindrical silica gel desiccant pill with a warning in red "DESICCANT SILICA GEL, DO NOT EAT". Each bottle also includes one piece of white polyurethane foam to offer the tablets protection while transportation.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Medochemie Ltd (Central Factory), 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. DATE OF REVISION OF THE TEXT

Nov 2021