SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Entacapone HEC 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg entacapone.

Excipient with known effect:
Each tablet contains 0.29 mg of Lecithin (Soya).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Orange-brown capsular-shaped film-coated tablets, debossed “S52” on one side and blank on the other side. The tablet size is 14 × 6.5 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 the levodopa 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 the 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 entacapone dose is 200 mg ten times daily (2000 mg).

Entacapone enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reactions such as dyskinesias, nausea, vomiting and hallucinations, it is often necessary to adjust the levodopa dose within days or weeks of initiating entacapone treatment. The daily dose of levodopa should be reduced by 10-30% either by reducing the amount of levodopa in each dose or by extending the dosing intervals, 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 by 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, patients receiving dialysis therapy may need a longer dosing interval (see section 5.2).

Patients with hepatic impairment:
See section 4.3.

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

Paediatric population:
The safety and efficacy of entacapone in children aged less than 18 years 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, peanut, 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 such as phenelzine and tranylcypromine.
- Concomitant use of a selective MAO-A inhibitor plus a selective MAO-B inhibitor and entacapone (see section 4.5).
- 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 (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 has been reported following controlled trials involving entacapone treatment in which entacapone has been discontinued abruptly. Since its 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-O-methyl transferase (COMT) such as 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 are also applicable to entacapone treatment. Entacapone increases the bioavailability of levodopa from standard

levodopa/benserazide preparations 5-10% more than from standard levodopa/carbidopa preparations. Consequently, undesirable 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 reduce the daily dose of levodopa by 10-30% either by reducing the amount of levodopa in each dose or by extending the dosing intervals, according to the clinical condition of the patient. (see sections 4.2 and 4.8).

Entacapone may aggravate levodopa-induced orthostatic hypotension and should, therefore, be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

In clinical studies, undesirable dopaminergic effects such as dyskinesia were more common in patients who received entacapone and dopamine agonists such as bromocriptine, selegiline or amantadine than in those who received placebo in 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 onset sleep 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, the monitoring of bodyweight is recommended in order to avoid possible excessive weight loss. Prolonged or persistent diarrhoea during entacapone treatment 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 such as 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. A review of treatment is recommended if such symptoms develop.

A general medical evaluation, including liver function tests, should be considered for patients who experience progressive anorexia, asthenia and weight loss within a relatively short period.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of entacapone with carbidopa has been observed when using the recommended treatment schedule. Pharmacokinetic consequences of combination with benserazide have 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, experience of the concurrent 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 such as 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 4.4). 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 interfere with the metabolism of medicinal products which is 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% [CI_{90} 11–26%]. The INR values increased on average by 13% [CI_{90} 6–19%]. Thus, monitoring INR is recommended when entacapone treatment is initiated in 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 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 during treatment.

Patients receiving entacapone and levodopa and presenting with somnolence and/or sudden onset sleep 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

a. 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 the levodopa dose decreases the severity and frequency of these reactions. The other major class of adverse reactions is gastrointestinal 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 such as diarrhoea (2.5%) and increased dopaminergic adverse reactions of levodopa such as 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 2,000mg per day) than with lower doses of entacapone.

b. Tabulated list of adverse reactions

The adverse reactions listed in Table 1 have been accumulated from both clinical studies and post-marketing surveillance.

Table 1. Adverse drug reactions *

Psychiatric disorders		
	Common:	Insomnia, hallucinations, confusion, paranoia
	Very rare:	Agitation
Nervous system disorders		
	Very common:	Dyskinesia
	Common:	Parkinsonism exacerbation, dizziness, dystonia, hyperkinesia
Cardiac disorders**		
	Common:	Ischemic 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
	Not known:	Colitis
Hepatobiliary disorders		
	Rare:	Hepatic function tests abnormal
	Not known:	Hepatitis with mainly cholestatic features (see section 4.4.)
Skin and subcutaneous tissue disorders		
	Rare:	Erythematous or maculopapular rash
	Very rare:	Urticaria
	Not known:	Skin, hair, beard and nail discolorations
Renal and urinary disorders		
	Very common:	Urine discoloration
General disorders and administration site conditions		
	Common:	Fatigue, increased sweating, fall
	Very rare:	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 entacapone studies involving 2082 patients with end-of-dose motor fluctuations.

c. 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: Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as entacapone in association with levodopa, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating and compulsive eating (see section 4.4). Isolated cases of NMS have been reported following the 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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The post-marketing data include isolated cases of overdose in which the reported highest daily dose of entacapone has been 16,000mg. The acute symptoms and signs of overdose in these cases 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, 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 (hr) was measured from home diaries and in study II, the proportion of daily On time was measured.

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	
Weeks 8-24	10.7±2.2	9.4±2.6	1 hr 20 min (8.3%) $CI_{95\%}$ 45 min, 1 hr 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	
Weeks 8-24	66.8±14.5	62.8±16.80	4.5% (0 hr 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 inter-individual variations in the absorption of entacapone.

The peak concentration (C_{max}) in plasma is usually reached about one hour after ingestion of a 200mg 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 800ml/min.

Entacapone is extensively bound to plasma proteins, mainly albumin. In the therapeutic concentration range the unbound fraction in human plasma is about 2%. At therapeutic concentrations, entacapone does not displace other extensively bound substances such as 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}~4μM). Entacapone showed little or no inhibition of other types of P450 isoenzyme (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 portion (95%) of the product excreted in urine is conjugated with glucuronic acid. Of the metabolites found in urine only about 1% has been formed through oxidation.

Characteristics in patients
The pharmacokinetic properties of entacapone are similar in both young and old 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 the iron chelating properties of entacapone, was observed. In

reproductive toxicity studies, decreased foetal weight and slightly delayed bone development were noticed in rabbits dosed in the therapeutic range.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Mannitol
Sodium Starch Glycolate (type A)
Povidone (K29/32)
Magnesium Stearate

Film-coating:
Polyvinyl Alcohol (Partly hydrolyzed)
Talc
Titanium Dioxide (E171)
Macrogol 3350
Iron Oxide Yellow (E172)
Lecithin (Soya)
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of HDPE bottle with a child-resistant and tamper-evident bottle packaging system consists of a polypropylene cap which includes an outer cap, a white child-resistant cap and a liner with two piece pulp-backed heat induction foil innerseal.
30, 100 or 175 film-coated tablets in a bottle, 30, 90, 100 or 175 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

HEC Pharm GmbH
Gabriele-Tergit-Promenade 17
10963 Berlin

8 MARKETING AUTHORISATION NUMBER(S)

PL 41987/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/09/2018

10 DATE OF REVISION OF THE TEXT

19/12/2018