TABLE OF CONTENTS – CLEAN PROPOSED PROFESSIONAL INFORMATION MARCH 2026

TABLE OF CONTENTS – CLEAN PROPOSED PROFESSIONAL INFORMATION MARCH 2026

TABLE OF CONTENTS – CLEAN PROPOSED PROFESSIONAL INFORMATION MARCH 2026 1

CLEAN PROPOSED PROFESSIONAL INFORMATION MARCH 2026 2

SCHEDULING STATUS 2

1. NAME OF THE MEDICINE 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION 2

3. PHARMACEUTICAL FORM 2

4. CLINICAL PARTICULARS 2

4.1 Therapeutic indications 2

4.2 Posology and method of administration 3

4.3 Contraindications 4

4.4 Special warnings and precautions for use 4

4.5 Interaction with other medicines and other forms of interaction 6

4.6 Fertility, pregnancy and lactation 7

4.7 Effects on ability to drive and use machines 8

4.8 Undesirable effects 8

4.9 Overdose 10

5. PHARMACOLOGICAL PROPERTIES 11

5.1 Pharmacodynamic properties 11

5.2 Pharmacokinetic properties 11

6. PHARMACEUTICAL PARTICULARS 13

6.1 List of excipients 13

6.2 Incompatibilities 13

6.3 Shelf life 13

6.4 Special precautions for storage 13

6.5 Nature and contents of container 13

6.6 Special precautions for disposal and other handling 13

7. HOLDER OF CERTIFICATE OF REGISTRATION 14

8. REGISTRATION NUMBER(S) 14

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 14

10. DATE OF REVISION OF THE TEXT 14

CLEAN PROPOSED PROFESSIONAL INFORMATION MARCH 2026

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ENKOBIST 200 Entacapone 200 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ENKOBIST 200** film-coated tablet contains 200 mg entacapone.

Sugar free

For a full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film-coated tablet

ENKOBIST 200: Brown coloured, oval shaped, biconvex, film coated tablets debossed with “L 7” on one side and plain surface on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENKOBIST 200 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.

4.2 Posology and method of administration

Posology:

Adults:

ENKOBIST 200 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 **ENKOBIST 200.**

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 g of entacapone.

ENKOBIST 200 enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reaction, e.g. dyskinesias, nausea, vomiting and hallucinations, it is often necessary to adjust levodopa dosage within the first few days to first few weeks after initiating treatment with **ENKOBIST 200**. The daily dose of levodopa should be reduced by about 10 to 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 **ENKOBIST 200** 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.

ENKOBIST 200 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 **ENKOBIST 200** is initiated.

Special populations

Renal insufficiency does not affect the pharmacokinetics of **ENKOBIST 200** 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**).

Elderly

No dosage adjustment of **ENKOBIST 200** is required for elderly patients.

Paediatric population

The safety and efficacy of **ENKOBIST 200** in children below the age of 18 years have not been established.

Method of administration

ENKOBIST 200 is administered orally and simultaneously with each levodopa/carbidopa or levodopa/benserazide dose.

ENKOBIST 200 can be taken with or without food (see **section 5.2**).

4.3 Contraindications

ENKOBIST 200 is contraindicated in patients with:

- Hypersensitivity to entacapone or to any of the excipients of the medicine (see **section 6.1**).
- Liver impairment.
- Patients with pheochromocytoma due to the increased risk of hypertensive crisis.
- Concomitant use of **ENKOBIST 200** 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 **ENKOBIST 200** (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 **ENKOBIST 200** treatment.

NMS, including rhabdomyolysis and hyperthermia, is characterized by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g. agitation, contusion, coma), hyperthermia, autonomic dysfunction

(tachycardia, labile blood pressure) and elevated serum creatine phosphokinase (CPK). 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 **ENKOBIST 200** and other dopaminergic medications. When considered necessary, withdrawal of **ENKOBIST 200** and other dopaminergic treatment should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of **ENKOBIST 200**, an increase in levodopa dosage may be necessary.

Because of its mechanism of action, **ENKOBIST 200** may interfere with the metabolism of medicines containing a catechol group and potentiate their action. Thus, **ENKOBIST 200** should be administered cautiously to patients being treated with medicines metabolised by COMT, e.g. rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, and apomorphine (see **Section 4.5**).

ENKOBIST 200 is always given as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for **ENKOBIST 200** treatment. **ENKOBIST 200** increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5-10 % more than from standard levodopa/carbidopa preparations. Consequently, undesirable dopaminergic effects may be more frequent when **ENKOBIST 200** is added to levodopa/benserazide treatment (see **section 4.8**). To reduce levodopa-related dopaminergic adverse effects, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating **ENKOBIST 200** treatment, according to the clinical condition of the patient (see **Sections 4.2 and 4.8**).

ENKOBIST 200 may aggravate levodopa-induced orthostatic hypotension. **ENKOBIST 200** should be given cautiously to patients who are taking other medicines products which may cause orthostatic hypotension.

In clinical studies, undesirable dopaminergic effects, e.g. dyskinesia, were more common in patients who received **ENKOBIST 200** and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to those who received placebo with this combination. The doses of other antiparkinsonian medications may need to be adjusted when **ENKOBIST 200** treatment is initiated.

Isolated cases of hepatitis with cholestatic features have been reported.

ENKOBIST 200 used in combination 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.

For patients experiencing diarrhoea, monitoring 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.

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.

Pathological gambling, increased libido and hyper sexuality have been reported in Parkinson's disease patients treated with **ENKOBIST 200** in association with levodopa.

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

4.5 Interaction with other medicines and other forms of interaction

No interaction of **ENKOBIST 200** 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 inrepeated-dose studies in parkinsonian patients.

However, the experience of the clinical use of entacapone with several medicines, including MAO-A inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors such asdesipramine, maprotiline and venlafaxine, and medicines 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 medicines are used concomitantly with **ENKOBIST 200** (see also **sections 4.3 and 4.4**).

ENKOBIST 200 may be used with selegiline (a selective MAO-B inhibitor), but the daily dose of selegiline should not exceed 10 mg.

ENKOBIST 200 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 medicines, including diazepam and ibuprofen. Clinical interaction studies with diazepam and non-steroidal anti-inflammatory medicines have not been carried out. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicines.

Due to its affinity to cytochrome P450 2C9 *in vitro* (see **section 5.2**), entacapone may potentially interfere with medicines with metabolism dependent on this isoenzyme, such as S-warfarin. Thus, more frequent monitoring of INR is recommended when **ENKOBIST 200** is initiated for patients receiving warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use in pregnancy has not been established. As there is no experience in pregnant women, **ENKOBIST 200** should not be used during pregnancy.

Lactation

Safety of use during lactation has not been established. In animal studies entacapone was excreted in milk. The safety of entacapone in infants is unknown. The safety of entacapone in infants is unknown. Women should not breastfeed during treatment with **ENKOBIST 200**.

4.7 Effects on ability to drive and use machines

ENKOBIST 200 in association with levodopa may have major influence on the ability to drive and use machines. **ENKOBIST 200** may, together with levodopa cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines. Patients being treated with **ENKOBIST 200** in association with levodopa and presenting with somnolence and/or sudden sleep on setepisodes 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.

4.8 Undesirable effects

Summary of the reported safety profile

Most of the undesirable effects caused by **ENKOBIST 200** relate to the increased dopaminergic activity and occur most commonly at the beginning of the treatment. Reduction of levodopa dosage may decrease the severity and frequency of these events.

Usually undesirable effects caused by **ENKOBIST 200** are mild to moderate. The most common undesirable effects leading to discontinuation of entacapone treatment have been gastrointestinal symptoms and dopaminergic symptoms (e.g dyskinesias).

Some of the adverse reactions, such as dyskinesia, nausea, and abdominal pain, may be more common with the higher doses (1,4 to 2 g per day) than with the lower doses of **ENKOBIST 200**.

Tabulated summary of adverse events

System organ class	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	Frequency unknown	Decrease in haemoglobin, erythrocyte count and haematocrit
Psychiatric disorders	Frequent	Insomnia, hallucinations, confusion, paroniria

	Less frequent	Agitation
Nervous system disorders	Frequent	Dyskinesia, Parkinsonism aggravated, dizziness, dystonia, hyperkinesia, headache, tremor
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Frequent	Ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris)
	Less frequent	Myocardial infarction
Vascular disorders	Frequent	Postural hypotension
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, abdominal pain, dry mouth, constipation, vomiting
	Less frequent	Anorexia
	Frequency unknown	Colitis
Hepatobiliary disorders	Less frequent	Hepatic function tests abnormal
	Frequency unknown	Hepatitis with mainly cholestatic features (see **Section 4.4**)
Skin and subcutaneous tissue disorders	Less frequent	Erythematous or maculopapular rash, urticaria
	Frequency unknown	Skin, hair, beard and nail discolourations
Musculoskeletal, connective tissue and bone disorders	Frequent	Leg cramps
Renal and urinary disorders	Frequent	Urine discolouration

General disorders and administration site conditions	Frequent	Fatigue, sweating increased, fall
	Less frequent	Weight decrease

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

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 **ENKOBIST 200** 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com. By reporting side effects, you can help provide more information on the safety of **ENKOBIST 200**.

4.9 Overdose

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

Category and Class: A 5.4.1 Anti-parkinsonism preparations

ATC code: N04BX02

5.1 Pharmacodynamic properties

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 indicating the reversible nature of COMT inhibition.

5.2 Pharmacokinetic properties

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 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 (Vdss). 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 P4502C9 (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 people and elderly. The metabolism of the medicine 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains microcrystalline cellulose, corn starch, croscarmellose sodium, povidone, magnesium stearate and film coating containining hypromellose, titanium dioxide (CI 77891), propylene glycol, talc, red iron oxide (CI 77492) and yellow iron oxide (CI 77491).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Round, white HDPE container with screw neck with white child-resistant polypropylene closure with pulp and heat seal liner.

Pack size 100 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

49/5.4.1/1067

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2022

10. DATE OF REVISION OF THE TEXT

13 October 2022

PM0271-01

