

 **13 June 2025**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Levodopa Carbidopa Entacapone "Neuraxpharm", film-coated tablets**

**0. D.SP.NO.**

33504

**1. NAME OF THE MEDICINAL PRODUCT**

Levodopa Carbidopa Entacapone "Neuraxpharm"

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

50 mg/12.5 mg/200 mg

Each film-coated tablet contains 50 mg of levodopa, 12.5 mg of carbidopa and 200 mg of entacapone.

75 mg/18.75 mg/200 mg

Each film-coated tablet contains 75 mg of levodopa, 18.75 mg of carbidopa and 200 mg of entacapone.

100 mg/25 mg/200 mg

Each film-coated tablet contains 100 mg of levodopa, 25 mg of carbidopa and 200 mg of entacapone.

125 mg/31.25 mg/200 mg

Each film-coated tablet contains 125 mg of levodopa, 31.25 mg of carbidopa and 200 mg of entacapone.

150 mg/37.5 mg/200 mg

Each film-coated tablet contains 150 mg of levodopa, 37.5 mg of carbidopa and 200 mg of entacapone.

175 mg/43.75 mg/200 mg

Each film-coated tablet contains 175 mg of levodopa, 43.75 mg of carbidopa and 200 mg of entacapone.

200 mg/50 mg/200 mg

Each film-coated tablet contains 200 mg of levodopa, 50 mg of carbidopa and 200 mg of entacapone.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablets

50 mg/12.5 mg/200 mg

Brown coloured, round shaped, biconvex, film coated tablets, debossed with "M71" on one side and plain surface on the other side with a diameter of approximately 10 mm approximately.

75 mg/18.75 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M72" on one side and plain surface on the other side with a length of 13.9 mm and a width of 7.9 mm approximately.

100 mg/25 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M73" on one side and plain surface on the other side with a length of 16 mm and a width of 7.5 mm approximately.

125 mg/31.25 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M74" on one side and plain surface on the other side with a length of 14.2 mm and a width of 9.2 mm approximately.

150 mg/37.5 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M75" on one side and plain surface on the other side with a length of 14.2 mm and a width of 9.2 mm approximately.

175 mg/43.75 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M76" on one side and plain surface on the other side with a length of 17 mm and a width of 7.7 mm approximately.

200 mg/50 mg/200 mg

Brown coloured, oval shaped, biconvex, film coated tablets, debossed with "M70" on one side and plain surface on the other side with a length of 17 mm and a width of 7.7 mm approximately.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Levodopa Carbidopa Entacapone "Neuraxpharm" is indicated for the treatment of adult patients with Parkinson’s disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

**4.2 Posology and method of administration**

Posology

The optimum daily dose must be determined by careful titration of levodopa in each patient. The daily dose should be preferably optimised using one of the seven available tablet strengths (50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg, 150 mg/37.5 mg/200 mg, 175 mg/43.75 mg/ 200 mg or 200 mg/50 mg/200 mg levodopa/carbidopa/entacapone).

Patients should be instructed to take only one Levodopa Carbidopa Entacapone "Neuraxpharm" tablet per dose administration. Patients receiving less than 70‑100 mg carbidopa a day are more likely to experience nausea and vomiting. While the experience with a total daily dose greater than 200 mg of carbidopa is limited, the maximum recommended daily dose of entacapone is 2,000 mg and therefore the maximum dose is ten tablets per day for the Levodopa Carbidopa Entacapone "Neuraxpharm" strengths of 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg and 150 mg/37.5 mg/200 mg. Ten tablets of Levodopa Carbidopa Entacapone "Neuraxpharm" 150 mg/37.5 mg/200 mg equals 375 mg of carbidopa a day. According to this daily carbidopa dose, the maximum recommended daily 175 mg/43.75 mg/ 200 mg dose is 8 tablets per day and Levodopa Carbidopa Entacapone "Neuraxpharm" 200 mg/50 mg/200 mg dose is 7 tablets per day.

Usually Levodopa Carbidopa Entacapone "Neuraxpharm" is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone.

*How to transfer patients taking levodopa/DDC inhibitor (carbidopa or benserazide) preparations and entacapone to Levodopa Carbidopa Entacapone "Neuraxpharm"*

*a.* Patients who are currently treated with entacapone and with standard release levodopa/carbidopa in doses equal to Levodopa Carbidopa Entacapone "Neuraxpharm" tablet strengths can be directly transferred to Levodopa Carbidopa Entacapone "Neuraxpharm" tablets of corresponding strength.

For example, a patient taking one tablet of 50 mg/12.5 mg of levodopa/carbidopa with one tablet of entacapone 200 mg four times daily can take one 50 mg/12.5 mg/200 mg Levodopa Carbidopa Entacapone "Neuraxpharm" tablet four times daily in place of their usual levodopa/carbidopa and entacapone doses.

*b*. When initiating Levodopa Carbidopa Entacapone "Neuraxpharm" therapy for patients currently treated with entacapone and levodopa/carbidopa in doses not equal to Levodopa Carbidopa Entacapone "Neuraxpharm" 50 mg/12.5 mg/200 mg (or 75 mg/18.75 mg/200 mg or 100 mg/25 mg/200 mg or 125 mg/31.25 mg/200 mg or 150 mg/37.5 mg/200 mg or 175 mg/43.75 mg/200 mg or 200 mg/50 mg/200 mg) tablets, Levodopa Carbidopa Entacapone "Neuraxpharm" dosing should be carefully titrated for optimal clinical response. At the initiation, Levodopa Carbidopa Entacapone "Neuraxpharm" should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.

*c*. When initiating Levodopa Carbidopa Entacapone "Neuraxpharm" in patients currently treated with entacapone and levodopa/benserazide in a standard release formulation, the dosing of levodopa/benserazide should be discontinued in the previous night, and Levodopa Carbidopa Entacapone "Neuraxpharm" should be started in the next morning. The starting dose of Levodopa Carbidopa Entacapone "Neuraxpharm" should provide either the same amount of levodopa or slightly (5-10%) more.

*How to transfer patients not currently treated with entacapone to Levodopa Carbidopa Entacapone "Neuraxpharm"*

Initiation of Levodopa Carbidopa Entacapone "Neuraxpharm" may be considered at corresponding doses to current treatment in some patients with Parkinson's disease and end-of-dose motor fluctuations, who are not stabilised on their current standard release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Levodopa Carbidopa Entacapone "Neuraxpharm" is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate treatment (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Levodopa Carbidopa Entacapone "Neuraxpharm".

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dose by 10-30% within the first days to first weeks after initiating Levodopa Carbidopa Entacapone "Neuraxpharm" treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

*Dose adjustment during the course of the treatment*

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Levodopa Carbidopa Entacapone "Neuraxpharm" should be considered, within the dose recommendations.

When less levodopa is required, the total daily dose of Levodopa Carbidopa Entacapone "Neuraxpharm" should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Levodopa Carbidopa Entacapone "Neuraxpharm" at an administration.

If other levodopa products are used concomitantly with a Levodopa Carbidopa Entacapone "Neuraxpharm" tablet, the maximum dose recommendations should be followed.

*Discontinuation of Levodopa Carbidopa Entacapone "Neuraxpharm" therapy:* If Levodopa Carbidopa Entacapone "Neuraxpharm" treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is transferred to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms.

*Paediatric population:* The safety and efficacy of Levodopa Carbidopa Entacapone "Neuraxpharm" in children aged below 18 years have not been established. No data are available.

*Elderly:* No dose adjustment of Levodopa Carbidopa Entacapone "Neuraxpharm" is required for older patients.

*Hepatic impairment:* It is advised that Levodopa Carbidopa Entacapone "Neuraxpharm" should be administered cautiously to patients with mild to moderate hepatic impairment. Dose reduction may be needed (see section 5.2). For severe hepatic impairment see section 4.3.

*Renal impairment:* Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, therefore Levodopa Carbidopa Entacapone "Neuraxpharm" therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapy (see section 5.2).

Method of administration

Each tablet is to be taken orally either with or without food (see section 5.2). One tablet contains one treatment dose and the tablet may only be administered as whole tablets.

**4.3 Contraindications**

- Hypersensitivity to the active substance, soya, peanut or to any of the excipients listed in section 6.1.

- Severe hepatic impairment.

- Narrow-angle glaucoma.

- Pheochromocytoma.

- Coadministration of Levodopa Carbidopa Entacapone "Neuraxpharm" with non‑selective monoamine oxidase (MAO‑A and MAO‑B) inhibitors (e.g. phenelzine, tranylcypromine).

- Coadministration with a selective MAO‑A inhibitor and a selective MAO‑B inhibitor (see section 4.5).

- A previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.

***Assessor’s comment***

*When compared to the originator, the Applicant is proposing hypersensitivity to soya and peanut as additional contraindications. The basis for including such additional contraindications is not clear and appropriate justification should be provided.*

**4.4 Special warnings and precautions for use**

- Levodopa Carbidopa Entacapone "Neuraxpharm" is not recommended for the treatment of drug‑induced extrapyramidal reactions.

- Levodopa Carbidopa Entacapone "Neuraxpharm" therapy should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease, history of peptic ulcer disease or history of convulsions.

- In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias; cardiac function should be monitored with particular care during the period of initial dose adjustments.

- All patients treated with Levodopa Carbidopa Entacapone "Neuraxpharm" should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current psychoses should be treated with caution.

- Concomitant administration of antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms.

- Patients with chronic wide‑angle glaucoma may be treated with Levodopa Carbidopa Entacapone "Neuraxpharm" with caution, provided the intra‑ocular pressure is well controlled and the patient is monitored carefully for changes in intra‑ocular pressure.

- Levodopa Carbidopa Entacapone "Neuraxpharm" may induce orthostatic hypotension. Therefore Levodopa Carbidopa Entacapone "Neuraxpharm" should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

- 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 section 4.7).

- In clinical studies, dopaminergic adverse 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 Levodopa Carbidopa Entacapone "Neuraxpharm" treatment is given.

- Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dose reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. 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. The early diagnosis is important for the appropriate management of NMS. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Neither NMS nor rhabdomyolysis have been reported in association with entacapone treatment from controlled trials in which entacapone was discontinued abruptly. Since the introduction of entacapone 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, the replacement of Levodopa Carbidopa Entacapone "Neuraxpharm" with levodopa and DDC inhibitor without entacapone or other dopaminergic treatment should proceed slowly and an increase in levodopa dose may be necessary.

- If general anaesthesia is required, therapy with Levodopa Carbidopa Entacapone "Neuraxpharm" may be continued for as long as the patient is permitted to take fluids and medicinal products by mouth. If therapy has to be stopped temporarily, Levodopa Carbidopa Entacapone "Neuraxpharm" may be restarted as soon as oral medicinal products can be taken at the same daily dose as before.

- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Levodopa Carbidopa Entacapone "Neuraxpharm".

- 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.

- 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 containing levodopa including Levodopa Carbidopa Entacapone "Neuraxpharm". Review of treatment is recommended if such symptoms develop.

- Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

- 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.

- Levodopa/carbidopa may cause a false positive result when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine. The use of glucose oxidase methods may give false negative results for glycosuria.

- This medicine contains less than 1 mmol (23 mg) sodium per maximum recommended daily dose, that is to say essentially ‘sodium-free’.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Other antiparkinsonian medicinal products*: To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian medicinal products with Levodopa Carbidopa Entacapone "Neuraxpharm" therapy. Entacapone in high doses may affect the absorption of carbidopa. However, no interaction with carbidopa has been observed with the recommended treatment schedule (200 mg of entacapone up to 10 times daily). Interactions between entacapone and selegiline have been investigated in repeated dose studies in Parkinson's disease patients treated with levodopa/DDC inhibitor and no interaction was observed. When used with Levodopa Carbidopa Entacapone "Neuraxpharm", the daily dose of selegiline should not exceed 10 mg.

Caution should be exercised when the following active substances are administered concomitantly with levodopa therapy.

*Antihypertensives*: Symptomatic postural hypotension may occur when levodopa is added to the treatment of patients already receiving antihypertensives. Dose adjustment of the antihypertensive agent may be required.

*Antidepressants:* Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants and levodopa/carbidopa. 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, paroxetine) is still limited. Caution should be exercised when these medicinal products are used concomitantly with Levodopa Carbidopa Entacapone "Neuraxpharm" (see also sections 4.3 and section 4.4).

***Assessor’s comment***

*The above paragraph on antidepressants is not aligned with the originator. The text should be aligned or a justification provided for the deviation.*

*Other active substances:* Dopamine receptor antagonists (e.g. some antipsychotics and antiemetics), phenytoin and papaverine may reduce the therapeutic effects of levodopa. Patients taking these medicinal products with Levodopa Carbidopa Entacapone "Neuraxpharm" should be carefully observed for loss of therapeutic response.

Due to entacapone's affinity to cytochrome P450 2C9 *in vitro* (see section 5.2), Levodopa Carbidopa Entacapone "Neuraxpharm" may potentially interfere with active substances whose metabolism is 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% [CI90 11‑26%]. The INR values were on average increased by 13% [CI90 6‑19%]. Thus, a control of INR is recommended when Levodopa Carbidopa Entacapone "Neuraxpharm" is initiated for patients receiving warfarin.

*Other forms of interactions:* Since levodopa competes with certain amino acids, the absorption of Levodopa Carbidopa Entacapone "Neuraxpharm" may be impaired in some patients on high protein diet.

Levodopa and entacapone may form chelates with iron in the gastrointestinal tract. Therefore, Levodopa Carbidopa Entacapone "Neuraxpharm" and iron preparations should be taken at least 2‑3 hours apart.

*In vitro data:* Entacapone binds to human albumin binding site II which also binds several other medicinal products, including diazepam and ibuprofen. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the medicinal products. Accordingly, to date there has been no indication of such interactions.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

There are no adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicity of the separate compounds (see section 5.3). The potential risk for humans is unknown. Levodopa Carbidopa Entacapone "Neuraxpharm" should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus.

Breastfeeding

Levodopa is excreted in human breast milk. There is evidence that breastfeeding is suppressed during treatment with levodopa. Carbidopa and entacapone were excreted in milk in animals but is not known whether they are excreted in human breast milk. The safety of levodopa, carbidopa or entacapone in the infant is not known. Women should not breast-feed during treatment with Levodopa Carbidopa Entacapone "Neuraxpharm".

Fertility

No adverse reactions on fertility were observed in preclinical studies with entacapone, carbidopa or levodopa alone. Fertility studies in animals have not been conducted with the combination of entacapone, levodopa and carbidopa.

**4.7 Effects on ability to drive and use machines**

No traffic warning.

Levodopa Carbidopa Entacapone "Neuraxpharm" may have major influence on the ability to drive and use machines. Levodopa, carbidopa and entacapone together may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

Patients being treated with Levodopa Carbidopa Entacapone "Neuraxpharm" 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 section 4.4).

**4.8 Undesirable effects**

**a. Summary of the safety profile**

The most frequently reported adverse reactions with levodopa/carbidopa/entacapone are dyskinesias occurring in approximately 19% of patients; gastrointestinal symptoms including nausea and diarrhoea occurring in approximately 15% and 12% of patients, respectively; muscle, musculoskeletal and connective tissue pain occurring in approximately 12% of patients; and harmless reddish-brown discolouration of urine (chromaturia) occurring in approximately 10% of patients. Serious events of gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been identified from the clinical trials with levodopa/carbidopa/entacapone or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur with levodopa/carbidopa/entacapone although no cases have been identified from the clinical trial data.

**b. Tabulated list of adverse reactions**

The following adverse reactions, listed in Table 1, have been accumulated both from a pooled data of eleven double-blind clinical trials consisting of 3230 patients (1810 treated with levodopa/carbidopa/entacapone or entacapone combined with levodopa/DDC inhibitor, and 1420 treated with placebo combined with levodopa/DDC inhibitor or cabergoline combined with levodopa/ DDC inhibitor), and from the post-marketing data since the introduction of entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor.

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).

**Table 1.** Adverse reactions

***Blood and lymphatic system disorders***

Common: Anaemia

Uncommon: Thrombocytopenia

***Metabolism and nutrition disorders***

Common: Weight decreased\*, decreased appetite\*

***Psychiatric disorders***

Common: Depression, hallucination, confusional state\*, abnormal dreams\*, anxiety, insomnia

Uncommon: Psychosis, agitation\*

Not known: Suicidal behaviour, Dopamine dysregulation syndrome

***Nervous system disorders***

Very common: Dyskinesia\*

Common: Parkinsonism aggravated (e.g. bradykinesia)\*, tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness\*, headache

Not known: Neuroleptic malignant syndrome\*

***Eye disorders***

Common: Blurred vision

***Cardiac disorders***

Common: Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris)\*\*, irregular heart rhythm

Uncommon: Myocardial infarction\*\*

***Vascular disorders***

Common: Orthostatic hypotension, hypertension

Uncommon: Gastrointestinal haemorrhage

***Respiratory, thoracic and mediastinal disorders***

Common: Dyspnoea

***Gastrointestinal disorders***

Very common: Diarrhoea\*, nausea\*

Common: Constipation\*, vomiting\*, dyspepsia, abdominal pain and discomfort\*, dry mouth\*

Uncommon: Colitis\*, dysphagia

***Hepatobiliary disorders***

Uncommon: Hepatic function test abnormal\*

Not known: Hepatitis with mainly cholestatic features (see section 4.4)\*

***Skin and subcutaneous tissue disorders***

Common: Rash\*, hyperhidrosis

Uncommon: Discolourations other than urine (e.g. skin, nail, hair, sweat)\*

Rare: Angioedema

Not known: Urticaria\*

***Musculoskeletal and connective tissue disorders***

Very common: Muscle, musculoskeletal and connective tissue pain\*

Common: Muscle spasms, arthralgia

Not known: Rhabdomyolysis\*

***Renal and urinary disorders***

Very common: Chromaturia\*

Common: Urinary tract infection

Uncommon: Urinary retention

***General disorders and administration site conditions***

Common: Chest pain, peripheral oedema, fall, gait disturbance, asthenia, fatigue

Uncommon: Malaise

\*Adverse reactions that are mainly attributable to entacapone or are more frequent (by the frequency difference of at least 1% in the clinical trial data) with entacapone than levodopa/DDC inhibitor alone. See *Description of selected adverse reactions* below.

\*\*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.

**c. Description of selected adverse reactions**

Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk in Table 1. Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat. Other adverse reactions with an asterisk in Table 1 are marked based on either their more frequent occurring (by the frequency difference of at least 1%) in the clinical trial data with entacapone than levodopa/DDCI alone or the individual case safety reports received after the introduction of entacapone into the market.

Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa therapy has not been established.

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 containing levodopa including Levodopa Carbidopa Entacapone "Neuraxpharm" (see section 4.4).

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

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

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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

The post-marketing data includes isolated cases of overdose in which the reported highest daily doses of levodopa and entacapone have been at least 10 000 mg and 40 000 mg, respectively. The acute symptoms and signs in these cases of overdose included agitation, confusional state, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration, discolourations of skin, tongue and conjunctiva, and chromaturia. Management of acute overdose with levodopa/carbidopa/entacapon therapy is similar to acute overdose with levodopa. Pyridoxine, however, is not effective in reversing the actions of levodopa/carbidopa/entacapon. Hospitalisation is advised and general supportive measures should be employed with immediate gastric lavage and repeated doses of charcoal over time. This may hasten the elimination of entacapone in particular by decreasing its absorption/reabsorption from the GI tract. The adequacy of the respiratory, circulatory and renal systems should be carefully monitored and appropriate supportive measures employed. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmias. If required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient has taken other active substances in addition to levodopa/carbidopa/entacapon should be taken into consideration. The value of dialysis in the treatment of overdose is not known.

**4.10 Legal status**

B

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: anti-parkinson drugs, dopa and dopa derivatives, ATC code: N04BA03.

According to the current understanding, the symptoms of Parkinson’s disease are related to depletion of dopamine in the corpus striatum. Dopamine does not cross the blood-brain barrier. Levodopa, the precursor of dopamine, crosses the blood brain barrier and relieves the symptoms of the disease. As levodopa is extensively metabolised in the periphery, only a small portion of a given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors.

Carbidopa and benserazide are peripheral DDC inhibitors which reduce the peripheral metabolism of levodopa to dopamine, and thus, more levodopa is available to the brain. When decarboxylation of levodopa is reduced with the co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse reactions such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, catechol-*O*-methyltransferase (COMT) becomes the major peripheral metabolic pathway catalyzing the conversion of levodopa to 3-Omethyldopa (3-OMD), a potentially harmful metabolite of levodopa. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased area under the curve (AUC) in the pharmacokinetic profile of levodopa. Consequently the clinical response to each dose of levodopa is enhanced and prolonged.

The evidence of the therapeutic effects of the combination of entacapone with levodopa/carbidopa is based on two phase III double-blind studies, in which 376 Parkinson’s disease patients with end-of-dose motor fluctuations received either entacapone or placebo with each levodopa/DDC inhibitor dose. Daily ON time with and without entacapone was recorded in home-diaries by patients. In the first study, entacapone increased the mean daily ON time by 1 h 20 min (CI95% 45 min, 1 h 56 min) from baseline. This corresponded to an 8.3% increase in the proportion of daily ON time. Correspondingly, the decrease in daily OFF time was 24% in the entacapone group and 0% in the placebo group. In the second study, the mean proportion of daily ON time increased by 4.5% (CI95% 0.93%, 7.97%) from baseline. This is translated to a mean increase of 35 min in the daily ON time. Correspondingly, the daily OFF time decreased by 18% on entacapone and by 5% on placebo. Because the effects of Levodopa Carbidopa Entacapone "Neuraxpharm" tablets are equivalent with entacapone 200 mg tablet administered concomitantly with the commercially available standard release carbidopa/levodopa preparations in corresponding doses these results are applicable to describe the effects of levodopa/carbidopa/entacapon as well.

**5.2 Pharmacokinetic properties**

*General characteristics of the active substances*

*Absorption/distribution:* There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone. Both levodopa and entacapone are rapidly absorbed and eliminated. Carbidopa is absorbed and eliminated slightly slower compared with levodopa. When given separately without the two other active substances, the bioavailability for levodopa is 15-33%, for carbidopa 40-70% and for entacapone 35% after a 200 mg oral dose. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone. The distribution volume of both levodopa (Vd 0.36-1.6 l/kg) and entacapone (Vdss 0.27 l/kg) is moderately small while no data for carbidopa are available.

Levodopa is bound to plasma proteins only to a minor extent of about 10-30% and carbidopa is bound approximately 36%, while entacapone is extensively bound to plasma proteins (about 98%) –mainly to serum albumin. At therapeutic concentrations, entacapone does not displace other extensively bound active 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 and elimination:* Levodopa is extensively metabolised to various metabolites: decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT) being the most important pathways.

Carbidopa is metabolized to two main metabolites which are excreted in the urine as glucuronides and unconjugated compounds. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone is almost completely metabolized prior to excretion via urine (10 to 20%) and bile/faeces (80 to 90%). The main metabolic pathway is glucuronidation of entacapone and its active metabolite,

the cis-isomer, which accounts for about 5% of plasma total amount.

Total clearance for levodopa is in the range of 0.55-1.38 l/kg/h and for entacapone is in the range of 0.70 l/kg/h. The elimination-half life is (t1/2) is 0.6-1.3 hours for levodopa, 2-3 hours for carbidopa and 0.4-0.7 hours for entacapone, each given separately.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs on repeated administration.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 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.

*Characteristics in patients*

*Elderly:* When given without carbidopa and entacapone, the absorption of levodopa is greater and elimination is slower in older subjects than in young subjects. However, after combination of carbidopa with levodopa, the absorption of levodopa is similar between the older and the young, but the AUC is still 1.5 fold greater in the older people due to decreased DDC activity and lower clearance by aging. There are no significant differences in the AUC of carbidopa or entacapone between younger (45–64 years) and older subjects (65–75 years).

*Gender:* The bioavailability of levodopa is significantly higher in women than in men. These differences are primarily explained by body weight, however a significant gender effect (higher concentrations in women) has been seen after correction for body weight.

***Assessor’s comment***

*The above paragraph on gender differences is not aligned with the originator. The text should be aligned or a justification provided for the deviation.*

*Hepatic impairment:* The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases (see sections 4.2 and 4.3). No particular studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment are reported, however, it is advised that Levodopa Carbidopa Entacapone "Neuraxpharm" should be administered cautiously to patients with mild or moderate hepatic impairment.

*Renal impairment*: Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. However, a longer dosing interval of Levodopa Carbidopa Entacapone "Neuraxpharm" may be considered for patients who are receiving dialysis therapy (see section 4.2).

**5.3 Preclinical safety data**

Preclinical data of levodopa, carbidopa and entacapone, tested alone or in combination, revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In repeated dose toxicity studies with entacapone, anaemia most likely due to iron chelating properties of entacapone was observed. Regarding reproduction toxicity of entacapone, decreased foetal weight and a slightly delayed bone development were noticed in rabbits treated at systemic exposure levels in the therapeutic range. Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see Section 4.6).

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Tablet core

Maltodextrin

Microcrystalline cellulose

Croscarmellose sodium

Colloidal silicon dioxide

Povidone (E1201)

Crospovidone

Magnesium stearate

Film coating

Hypromellose

Polysorbate 80

Titanium dioxide (E171)

Iron oxide red (E172)

Iron oxide yellow (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

4 years.

**6.4 Special precautions for storage**

50 mg/12.5 mg/200 mg film-coated tablets

75 mg/18.75 mg/200 mg film-coated tablets

125 mg/31.25 mg/200 mg film-coated tablets

150 mg/37.5 mg/200 mg film-coated tablets

175 mg/43.75 mg/200 mg film-coated tablets

This medicinal product does not require any special storage conditions.

100 mg/25 mg/200 mg film-coated tablets

200 mg/50 mg/200 mg film-coated tablets

Do not store above 30 °C.

**6.5 Nature and contents of container**

OPA/Aluminium/PVC/Aluminium-blister

Pack sizes: 100 and 130 film-coated tablets.

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. MARKETING AUTHORISATION HOLDER**

Neuraxpharm Sweden AB

P. O. Box 98

182 11 Danderyd

Sverige

**8. MARKETING AUTHORISATION NUMBER(S)**

50 mg/12.5 mg/200 mg: 69720

75 mg/18.75 mg/200 mg: 69722

100 mg/25 mg/200 mg: 69724

125 mg/31.25 mg/200 mg: 69725

150mg/37.5 mg/200 mg: 69726

175 mg/43.75 mg/200 mg: 69727

200 mg/50 mg/200 mg: 69729

**9. DATE OF FIRST AUTHORISATION**

13 June 2025

**10. DATE OF REVISION OF THE TEXT**

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