SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levodopa/Benserazide Orifarm 100 mg/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg levodopa and 28.5 mg benserazide hydrochloride corresponding to 25 mg benserazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Round, pale red tablets with a cross-score on both sides, 10 mm in diameter.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parkinson's disease (idiopathic). Postencephalitic Parkinsonism.

4.2 Posology and method of administration

Posology

Treatment with Levodopa/Benserazide Orifarm should be started gradually. The dose should be adjusted individually and titrated to reach the optimal effect. The following dose instructions should therefore be considered as a recommendation.

Initial therapy: In the early stages of Parkinson's disease, it is recommended to start the treatment with 50-100 mg levodopa 1-2 times daily. The dose should be increased by 50-100 mg per week divided into one or two dose increases. At a maintenance dose of 300-500 mg levodopa per day divided into 3-4 doses, the effect should be awaited and following that, the dose can be increased after a couple of months of treatment, if necessary.

Maintenance dose: A standard maintenance dose is 400-500 mg levodopa per day normally divided into 4 doses. In some patients, doses of up to 800 mg per day may be required to reach the full effect. The need for doses above 1000 mg per day is unusual and generally requires multiple dose increases. In some patients, especially elderly, an adequate antiparkinsonian effect may not be achieved due to dose-related side effects. In case of severe side effects, especially mental, the daily dose must be reduced or the treatment discontinued.

Patients with advanced disease: Problems with fluctuations in the therapeutic response (e. g. “end-of-dose deterioration” so-called wearing off effect and "on-and-off phenomenon") often occurs after several years of treatment. A more even plasma concentration of levodopa should be sought in these cases. The maintenance dose should be distributed over a larger number of administrations, up to 6-12 times per day. When combined with dopamine agonists or COMT inhibitors, the levodopa dose should generally be reduced.

Paediatric population
Children and adolescents: The safety of the use of levodopa/benserazide in patients under 25 years of age has not been established. Levodopa/Benserazide Orifarm should therefore not be given to patients under 25 years.

Method of administration
If possible, Levodopa/Benserazide Orifarm should be taken 30 minutes before or 1 hour after a meal to avoid that proteins from the diet compete with the uptake of levodopa and thus enable a rapid effect. Nausea and other discomfort in the gastrointestinal tract, which most often occurs during the initial treatment phase, may be reduced if Levodopa/Benserazide Orifarm is taken with a snack of low protein content (e.g. a biscuit) or liquid, or by a slow increase in the dose. Intake of Levodopa/Benserazide Orifarm with protein-rich foods may reduce the effect.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Levodopa/Benserazide Orifarm should not be given to patients with decompensated endocrine function (e.g. pheochromocytoma, hyperthyroidism, Cushing's syndrome), decompensated kidney or liver function, heart disease (e.g. severe heart arrhythmias and heart failure), psychiatric disorders with a psychotic component or narrow-angle glaucoma.

Levodopa/Benserazide Orifarm must not be co-administered with non-selective monoamine oxidase (MAO) inhibitors (see section 4.5). However, selective MAO-B inhibitors, such as selegiline or rasagiline, or selective MAO-A inhibitors, such as moclobemide, are not contraindicated. A combination of MAO-A and MAO-B inhibitors is equated with non-selective MAO inhibition and therefore this combination should not be co-administered with Levodopa/Benserazide Orifarm (see section 4.5).

Levodopa/Benserazide Orifarm should not be given to patients under 25 years of age (skeletal development must be complete).

Levodopa/Benserazide Orifarm should not be given to pregnant or fertile women who are not using a safe method of contraception. If a woman treated with Levodopa/Benserazide Orifarm becomes pregnant, the drug should be discontinued (after agreement with the doctor).

4.4 Special warnings and precautions for use

Much caution should be taken with organic dementia symptoms and a tendency to confusion.

Hypersensitivity reactions may occur in sensitive individuals.

It is recommended that the intraocular pressure is regularly measured in patients with open-angle glaucoma, as levodopa theoretically has the potential to increase the intraocular pressure.

Caution should be given when administering Levodopa/Benserazide Orifarm to patients with myocardial infarction, pre-existing coronary heart disease, coronary insufficiency, cardiac arrhythmias or heart failure (see section 4.3). In these patients, the monitoring of cardiac function should be carefully monitored at the start of treatment and during treatment there should be regular check-ups, which also includes ECG examination.

Careful monitoring is recommended for patients with risk factors for orthostatic hypotension (e.g. elderly patients, concomitant treatment with antihypertensive agents or other drugs with orthostatic effect) or with orthostatic hypotension in the anamnesis, especially at the beginning of treatment and in cases of dose increases.

It has been reported that levodopa/benserazide may cause decreased blood levels (e.g. hemolytic anemia, thrombocytopenia and leukopenia). In some cases, agranulocytosis and pancytopenia have been reported,

where a connection with levodopa/benserazide have not been established, but neither have been excluded. Regular blood tests should therefore be performed during treatment.

Depression may be part of the clinical picture in patients with Parkinson's disease, and may also occur in patients treated with levodopa/benserazide (see section 4.8) All patients treated with Levodopa/Benserazide Orifarm should be closely monitored in regard to the development of mental changes, depression with or without a suicidal tendency or other serious mental changes.

Levodopa/benserazide may induce dopaminergic dysregulation syndrome (DDS) which leads to excessive use of the drug. A small number of patients with Parkinson's disease are bothered by cognitive disorders and behavioural disorders that can be directly related to the fact that they have taken high doses of the drug compared to the recommended prescription and much above the doses required to treat their symptoms of Parkinson's disease.

If a patient needs anaesthesia, the normal Levodopa/Benserazide Orifarm treatment should continue as close to the operation as possible, except if halothane is to be used. When anesthetized with halothane Levodopa/Benserazide Orifarm treatment should be stopped 12-48 hours before the surgery because fluctuations of the blood pressure and/or arrhythmias may occur in patients treated with levodopa/benserazide. Levodopa/Benserazide Orifarm can be reintroduced after the operation and the dose should be gradually increased to the dose the patient received before surgery. In advanced Parkinson's disease and surgery with expected long-term postoperative care, treatment should be done in consultation with a neurologist.

Levodopa/Benserazide Orifarm treatment should not be stopped abruptly. Such discontinuation of the drug may lead to a condition similar to malignant neuroleptic syndrome (hyperpyrexia and muscle stiffness, possible mental changes and elevated serum creatinine phosphokinase, in more severe cases additional signs may include myoglobinuria, rhabdomyolysis and acute renal failure), which can be life-threatening. If a combination of these symptoms and signs occur, the patient should be kept under medical monitoring and, if necessary, hospitalized and receive prompt and appropriate symptomatic treatment. This may involve the reinstatement of Levodopa/Benserazide Orifarm after adequate evaluation.

Levodopa has been associated with somnolence and sudden sleep attacks. Sudden onset of sleep during daily activities, in some cases without warning signs, has been reported in rare cases. Patients should be informed of this and advised to exercise caution while driving or handling machines during treatment with levodopa. Patients who have exhibited somnolence and/or a sudden sleep attack must not be driving and handling machines. Dose reduction and/or discontinuation of treatment may be considered (see section 4.7).

Disturbed impulse control
Patients should be checked regularly for the development of disturbed impulse control. Patients and their caretakers should be alerted to behavioural symptoms that could indicate disturbed impulse control such as pathological gambling addiction, increased libido, hypersexuality, compulsive money spending and compulsive buying behaviour, binge eating and compulsive eating may occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa such as Levodopa/Benserazide Orifarm. If the patient develops these symptoms it is recommended that the treatment is reconsidered.

Laboratory tests
Regular checks of liver, kidney and cardiovascular function as well as blood values should be performed during treatment.

Patients with diabetes should undergo frequent tests of blood sugar and the dose of the antidiabetic medicine should be adjusted to the blood sugar level.

Malignant melanoma
Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma compared to the general population (about 2-6 times higher). It is unclear whether the increased risk observed was due to Parkinson's disease or other factors such as levodopa used to treat Parkinson's disease. Therefore, patients and healthcare professionals are advised to check for melanoma on a regular basis when

Levodopa/Benserazide Orifarm is used, regardless of the indication. Ideally, regular examinations of the skin should be done by a person with appropriate qualifications (e.g. dermatologist).

Levodopa/Benserazide Orifarm **contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Co-administration of the anticholinergic drug trihexyphenidyl with levodopa/benserazide reduces the rate, but not the extent, of the absorption of levodopa.

Iron sulphate reduces the maximum plasma concentration and AUC of levodopa by 30-50%. The pharmacokinetic changes observed with concomitant iron sulphate treatment appear to be clinically significant in some, but not all patients. Medicinal products containing divalent iron should not be taken at the same time as Levodopa/Benserazide Orifarm.

Metoclopramide increases the absorption rate of levodopa. The amount of levodopa absorbed is not affected.

Domperidone may increase the bioavailability of levodopa as a result of increased absorption of levodopa in the intestine.

Pharmacodynamic interactions
Neuroleptics, opioids and antihypertensive drugs containing reserpine are inhibiting levodopa/benserazide's mechanism of action.

Concomitant administration of antipsychotic drugs with dopamine receptor blocking properties, especially D2 receptor antagonists, may counteract the antiparkinsonian effect of levodopa/benserazide and should therefore be done with caution. Patients should be closely monitored for reduced antiparkinsonian effect and worsening of parkinsonian symptoms as well as reduced antipsychotic effect.

Symptomatic orthostatic hypotension occurred when combinations with levodopa and a decarboxylase inhibitors were added to the treatment in patients already receiving antihypertensive drugs. Levodopa/Benserazide Orifarm must be used with caution in patients receiving antihypertensive drugs. Blood pressure should be checked to allow for any dose adjustment of drugs if necessary.

Co-administration of levodopa/benserazide and sympathomimetics (drugs such as adrenaline, noradrenaline, isoprenaline or amphetamine which stimulate the sympathetic nervous system) may enhance the effect of sympathomimetics and therefore this combination is not recommended. If concomitant treatment is needed, close monitoring of the cardiovascular system is required and the dose of the sympathomimetic drug may need to be reduced.

If Levodopa/Benserazide Orifarm is given to patients treated with non-selective MAO-inhibitors, a period of at least 2 weeks should elapse between the discontinuation of the MAO-inhibitor and insertion of Levodopa/Benserazide Orifarm to avoid the risk of hypertensive crisis (see section 4.3). Selective MAO-B inhibitors such as selegiline and rasagiline, and selective MAO-A inhibitors, such as moclobemide, may be prescribed to patients treated with Levodopa/Benserazide Orifarm. However, it is recommended that the levodopa dose is adjusted individually according to the patient's needs, both in terms of efficacy and tolerability. A combination of MAO-A and MAO-B inhibitors is equated with non-selective MAO inhibitors, and therefore this combination should not be given together with Levodopa/Benserazide Orifarm (see section 4.3).

The combination with methyldopa may counteract the effect of levodopa in parkinsonism. In addition, levodopa may potentiate the undesirable cardiovascular effects of methyldopa.

The combination of levodopa with amitriptyline or imipramine may result in severe increase in blood pressure.

The combination with other Parkinson's disease drugs such as anticholinergics, amantadine, selegiline and dopamine agonists is permitted, but may potentiate both the desired and undesirable effects of the treatment. It may therefore be necessary to reduce the dose of Levodopa/Benserazide Orifarm or of the other medicine. When adjuvant therapy with a COMT inhibitor is initiated, dose reduction of Levodopa/Benserazide Orifarm may be necessary. Anticholinergics should not be discontinued abruptly when starting treatment with Levodopa/Benserazide Orifarm as it takes some time before the effects of levodopa shows.

Pyridoxine (vitamin B6) can be taken with Levodopa/Benserazide Orifarm because decarboxylase inhibitors, in this preparation benserazide, protect against peripheral metabolism of levodopa which would otherwise increase due to pyridoxine.

Phentiazine derivatives with piperazine ring or with dimethylaminopropyl chain and butyrophenone derivatives block the dopamine receptors in the brain and thereby counteract the effect of levodopa.

Levodopa may affect the results of laboratory tests for catecholamines, creatinine, uric acid and glucosuria. Levodopa can also cause false positive results for ketone bodies when test strips are used to control ketones in the urine.

Coomb's test may give a false positive answer in patients treated with levodopa/benserazide.

A reduction in the effect is seen when the drug is taken with a protein-rich meal. Levodopa is a large neutral amino acid and it competes with large neutral amino acids from proteins in the food for transport through the gastric mucosa and the blood-brain barrier.

Anesthesia with halothane: Levodopa/Benserazide Orifarm should be discontinued 12-48 hours before surgery requiring anesthesia with halothane as fluctuations in blood pressure and/or arrhythmias may occur.
For anesthesia with other anesthetics, see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
Available data from treatment of pregnant women with levodopa/benserazide are insufficient. Results from animal studies have shown a risk of disturbed skeletal development (see section 5.3).
The potential risk to the embryo or fetus is unknown. To rule out pregnancy, a pregnancy test is recommended before starting treatment.
Levodopa/benserazide is contraindicated during pregnancy and in women of childbearing potential not using a reliable method of contraception (see sections 4.3 and 5.3). Women of childbearing potential must use reliable contraception.

If pregnancy occurs, treatment with Levodopa/Benserazide Orifarm must be discontinued.

Breast-feeding
Significant levels of levodopa are excreted in human milk and it is unknown whether benserazide is excreted in human milk. Mothers treated with Levodopa/Benserazide Orifarm should not breast-feed as skeletal malformations in the baby cannot be ruled out.

4.7 Effects on ability to drive and use machines

Levodopa/benserazide may have a major influence on the ability to drive and use machines.
Patients being treated with levodopa and experiencing somnolence and/or sudden sleep attacks should be advised to refrain from driving or engaging in activities, as a reduced level of consciousness may expose themselves or others to the risk of serious injury or death (e.g. when handling machines), until the attacks or somnolence have ceased (see section 4.4).

4.8 Undesirable effects

For this medicinal product, there is no clinical documentation that can serve as a basis for a safe assessment of the frequency of adverse reactions.

The following side effects have been reported: 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).

Blood and lymphatic system disorders	
Rare	Hemolytic anemia Leukopenia Thrombocytopenia
Metabolism and nutrition disorders	
Common	Anorexia
Not known	Decreased appetite
Psychiatric disorders	
Common	Insomnia* Hallucination* Confusion Depression Psychotic reactions
Not known	Dopamine dysregulation syndrome (DDS) (see section 4.4) Agitation* Anxiety* Delusion* Disorientation* Pathological gambling Increased libido Hypersexuality Compulsive buying behavior Binge eating Eating disorder
Nervous system disorders	
Common	Hyperkinesia “On and off” effects
Rare	Neuroleptic malignant syndrome (when discontinuation of the medicine)
Not known	Ageusia Dysgensia Dyskinesia (choreiform and athetotic) Fluctuations in therapy response Freezing phenomenon Wearing off effect (end-of-dose deterioration) Somnolence Suddenly falling asleep
Cardiac disorders	
Common	Arrythmia
Vascular disorders	
Common	Orthostatic hypotension
Gastrointestinal disorders	
Common	Nausea Vomiting Diarrhea
Not known	Discolored saliva, tongue, teeth and oral mucosa

Hepatobiliary disorders	
Not known	Transaminases increased Alkaline phosphatase increased Gamma-GT increased
Skin and subcutaneous tissue disorders	
Rare	Pruritus Rash
Musculoskeletal and connective tissue disorders	
Not known	Restless leg syndrome
Renal and urinary disorders	
Not known	Urea blood level increased Chromaturia

* These side effects may especially occur in elderly patients and in patients with diseases in the anamnesis.

Description of selected side effects:

Psychiatric disorders
Psychiatric disorders can occur especially in elderly patients. Hyperkinesia is considered as a sign of overdose.

Disturbed impulse control
Pathological gambling, increased libido, hypersexuality, compulsive spending and compulsive buying behavior, binge eating and compulsive eating may occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa such as levodopa/benserazide (see section 4.4).

Central and peripheral nervous system
In later stages of treatment, dyskinesia (e.g. choreiform or atetotic movements) may occur. These side effects can usually be eliminated or tolerated by the patient by lowering the dose.

After long-term treatment fluctuations in therapy response may occur. These effects include freezing periods, end-of-dose deterioration and “on-off” effects and can usually be eliminated or tolerated by the patient through dose adjustment and by giving lower doses more frequently. Following an attempt to increase the dose again can be made to improve the therapeutic effect.

Levodopa/benserazide is associated with somnolence and has in very rare cases been associated with excessive somnolence during the day as well as somnolence with sudden sleep attacks.

Vascular disorders
Orthostatic disorders usually improve after reduction of the levodopa/benserazide dose.

Gastrointestinal disorders
Side effects from the gastrointestinal tract, which may occur early in treatment, can be greatly reduced if levodopa/benserazide is taken with a low-protein snack or liquid.. In order to reduce the side effects it is necessary to increase the dose slowly during dose adjustment. The side effects are generally dose dependent and disappears or decreases after dose reduction, thus the treatment may not need to be discontinued.

Musculoskeletal and connective tissue disorders
Restless legs syndrome
Development of augmentation (time shift of symptoms from evening/night to early afternoon/evening before taking the next night dose) is the most common side effect of long-term dopaminergic treatment.

Examinations
The urine can change color, usually to a reddish color that will turn dark if left to stand.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
Symptoms and signs of overdose are qualitatively similar to the side effects of levodopa/benserazide at therapeutic doses, but may be of greater severity. Overdose may cause cardiovascular side effects (e.g. cardiac arrhythmia), mental disorders (e.g. confusion and insomnia), gastrointestinal effects (e.g. nausea and vomiting) and abnormal involuntary movements (see section 4.8).

Treatment
Monitor the patient's vital signs and begin supportive care appropiate to the patient's clinical status. In particular, patients may need symptomatic treatment for the cardiovascular effects (e.g. antiarrhythmics) or central nervous system effects (e.g. respiratory stimulants, neuroleptics). Gastric emptying.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-parkinson drugs, ATC code: N04BA02.

Mechanism of action
Dopamine acts as a neurotransmitter in the brain, but is not present in high enough concentrations in the basal ganglia of Parkinson's patients. Levodopa or L-DOPA (3,4 dihydroxy L-phenylalanine) is an intermediate in dopamine biosynthesis. Levodopa (dopamine precursor) is used as a prodrug to raise dopamine levels, as it can cross the blood-brain barrier while dopamine cannot. Once levodopa has entered the central nervous system (CNS), it is metabolized to dopamine by aromatic L-amino decarboxylic acid.

Levodopa is decarboxylated to dopamine in both extracerebral and cerebral tissue after administration. As a result, most levodopa is not available for the basal ganglia and peripherally produced dopamine often causes unwanted effects. It is therefore desirable that the extracerebral decarboxylation of levodopa is inhibited. This effect is achieved by co-administration of benserazide, a peripheral decarboxylase inhibitor.
Levodopa/Benserazide Orifarm is a combination of levodopa and benserazide in a ratio of 4:1.

5.2 Pharmacokinetic properties

Benserazide:

Absorption
About 70 % of benserazide is absorbed via oral administration.

Distribution
Maximum plasma concentration is reached within one hour.

Elimination
About 60% of the dose given is excreted in the urine, the majority of which, about 85%, during the first 12 hours.

Levodopa:

Absorption
Following oral administration of levodopa, maximum plasma levels are reached within 1-2 hours.

Food intake reduces the absorption of levodopa by about 15%, and the C_{max} is 30% lower and occurs later, when Levodopa/Benserazide Orifarm tablets are administered with a standard meal.

Elimination
The excretion is mainly via the urine. Within a day about 80% of the dose given has been eliminated.

Pharmacokinetic/pharmacodynamic relationships
The same plasma level of levodopa is obtained with one-fifth of the levodopa dose in combination with benserazide in a ratio of 4:1. The frequency of side effects caused by extracerebrally formed dopamine is reduced. This especially applies to side effects such as nausea and vomiting.

Elderly
In elderly patients (65-78 years), the half-life and AUC of levodopa is approximately 25% higher than in younger patients. This difference is not considered clinically relevant.

5.3 Preclinical safety data

Levodopa/benserazide were not mutagenic in the Ames test. Carcinogenicity studies with levodopa/benserazide have not been performed. No animal fertility studies have been performed with levodopa/benserazide.
Teratogenicity studies showed no teratogenic effects in mice at doses up to 400 mg/kg, in rats at doses up to 600 mg/kg and rabbits at doses up to 120 mg/kg. At maternally toxic doses, intrauterine death increased (rabbit) and/or decreased fetal weight (rat).

General toxicological studies in rats have shown a risk of impaired skeletal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Docusate sodium
Iron oxide, red (E172)
Ethylcellulose (E462)
Silica, colloidal anhydrous
Cellulose, microcrystalline (E460)
Starch, pregelatinized
Mannitol (E421)
Calcium hydrogen phosphate, anhydrous (E341)
Crospovidone (E1202)
Magnesium stearate (E470 b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original bottle and keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle with child-resistant PE cap and a silica gel cannister.

Pack sizes
20, 30, 50, 60 and 100 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-12-16