SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levodopa/benserazide 50 mg/12.5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg levodopa and 12.5 mg benserazide (as hydrochloride).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

hard gelatin capsules filled with off-white to brownish white granules, with a grey opaque cap and blue opaque body, imprinted axially in black ink ’62.5’ on the cap and ‘BL’ on the body

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of Parkinson’s disease.

4.2 Posology and method of administration

Posology

Dosage and administration are variable and no more than a guide can be given.

The dose is dependent on the severity of extrapyramidal symptoms and individual tolerance. High single doses should be avoided.

Treatment must be initiated and the dose increased slowly, in order to limit the adverse events and so as not to reduce the likelihood of therapeutic success.

Standard dosage

For doses not practicable with this strength, other strengths of this medicinal product are available.

Patients not previously treated with levodopa

	Levodopa dose	Benserazide dose
Initial dose	100-200 mg	25-50 mg
Increase every 3rd to 7th day by	50-100 mg	12.5-25 mg
Maximum dose	800 mg	200 mg

Initially, each individual administration should not exceed 50 mg/12.5 mg. Subsequently, the daily dose should be divided into at least 4 administrations.

If undesirable effects occur (see section 4.8), the dose should first not be increased any further, or may be temporarily decreased and titrated again more slowly. If gastrointestinal undesirable effects occur, antiemetics such as domperidone may be administered.

The effective dose usually lies within the range of 400-800 mg levodopa/100-200 mg benserazide daily in divided doses, most patients requiring no more than 600 mg levodopa/150 mg benserazide daily.

Optimal improvement is usually seen in one to three weeks but the full therapeutic effect may not be apparent for some time. It is advisable, therefore, to allow several weeks to elapse before contemplating dosage increments above the average dose range. If satisfactory improvement is still not achieved, the dose may be increased but with caution and on a monthly basis. It is rarely necessary to give more than 800 mg levodopa/200 mg benserazide per day.

Treatment should be continued for at least six months before failure is concluded from the absence of a clinical response.

Patients previously treated with levodopa
Levodopa alone should be discontinued and levodopa/benserazide started after a treatment-free period of at least 12 hours. The levodopa dose in combination with benserazide should be approximately 20% of the previous dose of levodopa, in order to achieve a similar clinical effect. Observe the patient for one week and then, if necessary, increase the dosage in the manner described for new patients.

Patients previously treated with other levodopa / decarboxylase inhibitor combinations
Previous therapy should be withdrawn for 12 hours. In order to minimise the potential for any effects of levodopa withdrawal, it may be beneficial to discontinue previous therapy at night and institute levodopa/benserazide therapy the following morning. Initial and increasing doses should be administered in the manner described for patients not previously treated with levodopa.

Levodopa/benserazide may be used concomitantly in patients already on other antiparkinsonian treatment. As soon as the therapeutic effect of levodopa/benserazide becomes apparent, the dosage of the other treatment should be evaluated, and slowly reduced and withdrawn if necessary.

Special dosage recommendations

Patients who experience severe fluctuations in response may be helped by dividing

the dosage into smaller, more frequent doses (i.e. more than four times daily), without, however, altering the total daily dose.

Elderly
In the elderly, the dose must be titrated slowly.

Paediatric population
Levodopa/benserazide tablets are contraindicated in children and adolescents (see section 4.3).

Renal and hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic and renal impairment (creatinine clearance ≥ 30 ml/min) (see section 4.3).

Method of administration

Levodopa/benserazide capsules, hard are for oral use. They should be swallowed whole and must not be chewed.

When possible, levodopa/benserazide should be administered at least 30 minutes before or 1 hour after meals to avoid the competitive effect of dietary proteins on the absorption of levodopa and to enable a quicker response (see section 4.5). Gastrointestinal adverse reactions, which occur mainly in the early stages of treatment, can be controlled by taking the medicinal product with low protein food or liquid, or by slow dose titration.

Levodopa/benserazide must usually be taken over the long term (substitution therapy). If it is well tolerated, the treatment need not be limited in time.

4.3 Contraindications

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- decompensated endocrine function (e.g. phaeochromocytoma, hyperthyroidism, Cushing syndrome);
- severe renal or hepatic impairment;
- severe cardiac disorders (e.g. severe tachycardia, severe cardiac arrhythmias and cardiac failure);
- severe metabolic or bone marrow disorders;
- psychiatric diseases with a psychotic component;
- patients below 25 years of age (skeletal development must be complete);
- treatment with reserpine;
- treatment with non-selective monoamine oxidase (MAO) inhibitors or a combination of MAO A and MAO B inhibitors because of the potential for hypertensive crises (see section 4.5). Combination of MAO-A and MAO-B inhibitors are equivalent to non-selective MAO inhibition, and hence this combination should not be given concomitantly with levodopa-benserazide (see section 4.5);
- closed angle glaucoma;
- Levodopa/benserazide must not be given to pregnant women or to women of childbearing potential in the absence of adequate contraception (see section 4.6). If pregnancy occurs in a women taking levodopa/benserazide, the medicine must be discontinued (as advised by the prescribing physician).

4.4 Special warnings and precautions for use

Hypersensitivity reactions may occur in susceptible individuals.

Use of levodopa/benserazide is not recommended in the treatment of pharmacogenic extrapyramidal reactions or Huntington's chorea.

In the initial phase of treatment, hepatic, renal and haematopoietic function should be evaluated frequently, during extended therapy periodically.

Whenever therapy has been interrupted for longer periods, dosage should again be adjusted gradually; however, in many cases the patient can rapidly be returned to his previous therapeutic dosage.

Care should be exercised when levodopa/benserazide is administered to patients with pre-existing coronary artery disorders, cardiac arrhythmias or cardiac failure (see also section 4.3). Cardiac function should be monitored with particular care in such patients during the period of treatment initiation and regularly thereafter throughout treatment.

Close monitoring of patients with risk factors for (e.g. elderly patients, concomitant antihypertensives or other medication with orthostatic potential) or a history of orthostatic hypotension is recommended especially at the beginning of treatment or at dose increases. However, hypotonic circulatory disorders can, usually be controlled via a dose reduction of levodopa/benserazide.

Levodopa/benserazide has been reported to induce decreases in blood count (e.g. haemolytic anaemia, thrombocytopenia and leukopenia). In a few instances agranulocytosis and pancytopenia have been reported in which the association with levodopa/benserazide could neither be established, nor be completely ruled out. Therefore, patient's blood count should be monitored frequently during the initial phase of treatment and periodically thereafter throughout treatment.

Patients with a history of gastrointestinal ulceration, convulsions or osteomalacia should be monitored particularly carefully.

Gastrointestinal disorders
Undesirable gastrointestinal effects such as nausea, vomiting and diarrhoea, which may occur mainly in the early stages of the treatment, can largely be controlled by taking levodopa/benserazide with some low protein food or liquid or by increasing the dose slowly.

Open-angle glaucoma
Patients with open-angle glaucoma can be treated cautiously with levodopa/benserazide, provided that intra-ocular pressure is well controlled. Regular measurement of intraocular pressure is advisable in patients with open-angle glaucoma, as levodopa theoretically has the potential to raise intraocular pressure.

Dyskinesia (choreiform or athetotic)
At later stages of the treatment, dyskinesia (e.g. choreiform or athetotic, see dection 4.8) may occur and can usually be controlled by reducing the dose.

Fluctuations in therapeutic response

With prolonged treatment, fluctuations in therapeutic response may also be encountered. They include 'freezing' episodes, 'end-of-dose' deterioration and the 'on-off' effect (see section 4.8). These can usually be reduced or made tolerable by adjusting the dosage and by giving smaller single doses more frequently. An attempt at increasing the dosage again can subsequently be made in order to intensify the therapeutic effect (see section 4.2).

Depression
Depression can be part of the clinical picture in patients with Parkinson's disease and may also occur in patients treated with levodopa/benserazide. All patients should be carefully monitored for psychological changes and depression with or without suicidal ideation.

Dopamine dysregulation syndrome (DDS)
Levodopa/benserazide may induce dopamine dysregulation syndrome resulting in excessive use of the product. A small subgroup of PD patients suffer from cognitive and behavioural disturbance that can be directly attributed to taking increasing quantities of medication against medical advice and well beyond the doses required to treat their motor disabilities.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa, including levodopa/benserazide. Review of treatment is recommended if such symptoms develop.

Abrupt withdrawal
Levodopa-benserazide must not be withdrawn abruptly. Abrupt withdrawal of the preparation may result in a neuroleptic malignant-like syndrome (hyperpyrexia and muscular rigidity, possibly psychological changes and elevated serum creatinine phosphokinase, additional signs in severe cases may include myoglobinuria, rhabdomyolysis – and acute renal failure) which may be life-threatening. Should a combination of such symptoms and signs occur, the patient should be kept under medical surveillance, if necessary, hospitalized and rapid and appropriate symptomatic treatment given. This may include resumption of levodopa/benserazide therapy after an appropriate evaluation.

Pyridoxine (vitamin B6)
Pyridoxine (vitamin B6) may be given with levodopa/benserazide since the presence of a decarboxylase inhibitor protects against the peripheral levodopa transformation facilitated by pyridoxine.

Somnolence and episodes of sudden sleep onset
Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered (see section 4.7).

General anaesthetic
If a patient requires a general anaesthetic, the normal levodopa/benserazide regimen should be continued as close to the surgery as possible, except in the case of halothane. In general anaesthesia with halothane levodopa/benserazide should be discontinued 12 - 48 hours before surgical intervention as fluctuations in blood pressure and/or arrhythmias may occur in patients with co-administration of levodopa/benserazide and halothane. Levodopa/benserazide therapy

may be resumed following surgery; the dosage should be increased gradually to the preoperative level.

Malignant melanoma
Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold 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 providers are advised to monitor for melanomas on a regular basis when using levodopa/benserazide for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

Laboratory tests
Periodical evaluation of hepatic, renal and cardiovascular function and blood count should be performed periodically during treatment.

Patients with diabetes should undergo frequent blood sugar tests, and the dosage of antidiabetic agents should be adjusted to blood sugar levels.

4.5 Interaction with other medicinal products and other forms of interaction

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

Ferrous sulphate reduces the peak plasma concentration and area-under-the-curve (AUC) of levodopa by 30-50%. The pharmacokinetic changes observed during concomitant treatment with ferrous sulphate appear to reach clinical significante in some but not all patients.

Metoclopramide increases the rate of absorption of levodopa.

Domperidone may increase the bioavailability of levodopa as a result of increased absorption of levodopa in the intestine. The concomitant use of levodopa and domepridone may increase the risk of cardiac arrhythmia.

Pharmacodynamic interactions

Substances acting on the extrapyramidal motor system
Opioids, reserpine-containing antihypertensives and neuroleptics (except clozapine) may inhibit the action of levodopa/benserazide. The association of levodopa/benserazide and neuroleptics is not recommended. If necessary, the lowest dose of both products should be used.

Antipsychotics
Concomitant administration of antipsychotics with dopamine receptor-blocking properties, particularly D_2 receptor antagonists, may inhibit the effect of levodopa/benserazide and should be carried out with caution, and the patients should be carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms.

MAO inhibitors
If levodopa/benserazide is to be administered to patients receiving irreversible non-selective MAO inhibitors, an interval of at least 2 weeks should be allowed between cessation of the MAO inhibitor and the start of levodopa/benserazide therapy. Otherwise unwanted effects such

as hypertensive crises are likely to occur (see section 4.3). Selective MAO-B inhibitors, such as selegiline and rasagiline and selective MAO-A inhibitors, such as moclobemide, can be prescribed to patients on levodopa/benserazide. Selegiline may, in some cases, increase the anti-Parkinsonian effect of levodopa without triggering any harmful interactions.
It is recommended to readjust the levodopa dose to the individual patient's needs, in terms of both efficacy and tolerability. Combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO inhibition, and hence this combination should not be given concomitantly with levodopa/benserazide (see section 4.3).

Antihypertensive agents
Symptomatic postural hypotension occurred when combinations of levodopa and a decarboxylase inhibitor were added to the treatment of patients already receiving antihypertensives. Levodopa/benserazide needs to be introduced cautiously in patients receiving antihypertensive medication. Blood pressure needs to be monitored to allow for potential dosage adjustment of either of the medicines, if required.

Sympathomimetics
Concomitant administration of levodopa/benserazide with sympathomimetics (agents such as epinephrine, norepinephrine, isoproterenol or amphetamine which stimulate the sympathetic nervous system) may potentiate their effects, therefore these combinations are not recommended. Should concomitant administration prove necessary, close surveillance of the cardiovascular system is essential, and the dose of the sympathomimetic agents may need to be reduced.

Other antiparkinsonian agents
Combination with other antiparkinsonian agents such as anticholinergics, amantadine and dopamine agonists are permissible, though both the desired and the undesired effects of treatment may be intensified. It may be necessary to reduce the dosage of levodopa/benserazide or the other substance. When initiating an adjuvant treatment with a COMT inhibitor, a reduction of the dosage of levodopa/benserazide may be necessary. Anticholinergics should not be withdrawn abruptly when levodopa/benserazide therapy is instituted, as levodopa does not begin to take effect for some time.

High-protein meals
The concomitant ingestion of high-protein meals may reduce the effect of levodopa/benserazide, because levodopa is a large neutral amino acid (LNAA) and competes with LNAAs from dietary proteins for transport across the gastric mucosa and the blood-brain barrier.

Alterations in diagnostic laboratory tests
Levodopa/benserazide may interact with several diagnostic laboratory tests:
- catecholamine, creatinine, uric acid, glucose (in glucosuria), alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT, aspartate transaminase, AST), serum glutamic-pyruvic transaminase (SGPT, alanine transaminase, ALT), lactate dehydrogenase (LDH) and bilirubin determination;
- increased blood urea nitrogen (BUN) levels have been observed with levodopa/benserazide;
- false-positive ketone body determination by test strip (the reaction is unchanged if the urine is boiled);
- false-negative urine glucose determination by the glucose-oxidase method;
- false-positive Coombs test.

Note

General anaesthesia with halothane
If general anaesthesia with halothane is required, levodopa/benserazide capsules should be discontinued 12-48 hours before surgical intervention requiring general anaesthesia with halothane as fluctuations in blood pressure and/or arrhythmias may occur.

For general anaesthesia with other anaesthetics, see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
To rule out pregnancy, a pregnancy test is recommended prior to initiation of treatment. Levodopa/benserazide is contraindicated during pregnancy and in women of childbearing potential in the absence of adequate contraception (see section 4.3 and 5.3), as there is no experience in humans and reproductive toxicity has been described in animals for both active substances. Women of childbearing potential have to use effective contraception during treatment with levodopa/benserazide. If pregnancy occurs, levodopa/benserazide must be discontinued by gradually tapering off the dose.

Breast-feeding
Levodopa inhibits prolactin secretion and hence lactation. Since it is not known whether benserazide passes into breast milk, mothers requiring levodopa-benserazide treatment should not nurse their infants, since the occurrence of skeletal malformations in the infants cannot be excluded. If treatment with levodopa/benserazide is required during lactation, breast-feeding should be discontinued

Fertility
No studies on fertility have been conducted.

4.7 Effects on ability to drive and use machines

Levodopa/benserazide may significantly affect the ability to drive and use machines.

Patients who experience excessive daytime sleepiness and/or sudden onset sleep episodes during treatment with levodopa/benserazide must be be informed 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 and somnolence have resolved (see section 4.4).

4.8 Undesirable effects

The following undesirable effects have been reported to occur when levodopa/ benserazide is administered:

The frequencies of undesirable effects are ranked according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000; < 1/100), rare (≥ 1/10000; < 1/1000), very rare (< 1/10,000), not known (frequency cannot be estimated from the available data).

Infections and infestations	
Not known	Febrile infections, bronchitis, common cold
Blood and lymphatic system disorders	
Not known	Haemolytic anaemia, thrombocytopenia, leukopenia
Metabolism and nutrition disorders	
Not known	Decreased appetite
Psychiatric disorders	
Not known	Dopamine dysregulation syndrome (DDS), confusional state, depression, agitation*, anxiety*, insomnia*, hallucinations*, delusions*, disorientation*, pathological gambling, increased libido, hypersexuality, compulsive shopping, binge eating, eating disorder symptom
Nervous system disorders	
Not known	Ageusia, dysgeusia, dyskinesia (choreiform or athetotic), Fluctuations in therapeutic response ('Freezing' phenomenon, 'End-of-dose' deterioration, 'On-off' phenomena), somnolence, excessive daytime somnolence, sudden onset of sleep, dizziness, headache, dry mouth
Cardiac disorders	
Not known	Arrhythmia
Vascular disorders	
Not known	Orthostatic hypotension
Gastrointestinal disorders	
Not known	Nausea, vomiting, diarrhoea, saliva discolouration, tongue discolouration, tooth discolouration, oral mucosa discolouration
Hepatobiliary disorders	
Not known	Alkaline phosphatase increased, transaminases increased, gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	
Not known	Pruritus, rash
Renal and urinary disorders	
Not known	Blood urea increased, chromaturia

* These events may occur particularly in elderly patients and in patients with a history of such disorders.

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/benserazide (see section 4.4).

Nervous system disorder

At later stages of the treatment, dyskinesia (e.g. choreiform or athetotic) may occur (see section 4.4). These can usually be eliminated or be made tolerable by a reduction of dosage.

With prolonged treatment, fluctuations in therapeutic response may also be encountered.

They include 'freezing' episodes, 'end-of-dose' deterioration and the 'on-off" effect (see section 4.4). These can usually be eliminated or made tolerable by adjusting the dosage and by giving smaller single doses more frequently. An attempt at increasing the dosage again can subsequently be made in order to intensify the therapeutic effect.

Levodopa/benserazide has been associated with tiredness and very rarely with excessive daytime somnolence and sudden sleep onset episodes (see section 4.4).

Vascular disorders
Orthostatic disorders commonly improve following reduction of the levodopa/benserazide dosage.

Gastrointestinal disorders
Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking levodopa/benserazide with some low protein food or liquid or by increasing the dose slowly.

Investigations
Urine may be altered in colour, usually acquiring a red tinge which turns dark on standing. Other body fluids or tissues may also be discoloured or stained including saliva, the tongue, teeth or oral mucosa.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs
Symptoms and signs of overdosage are qualitatively similar to the side-effects of levodopa/benserazide in therapeutic doses but may be of greater severity. Overdose may lead to cardiovascular side effects (e.g. cardiac arrhythmias), psychiatric disturbances (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 institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiovascular effects (e.g. antiarrhythmics) or central nervous system effects (e.g. respiratory stimulants, neuroleptics).

There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drug, levodopa and decarboxylase inhibitor
ATC code: N04B A02

The amino acid levodopa is used to substitute for dopamine deficiency in Parkinson's disease. Owing to the fact that at least 95% of orally administered levodopa is decarboxylated in extracerebral organs (intestines, liver, kidneys, heart, stomach), only small amounts reach the central nervous system after administration of levodopa monotherapy. The extracerebral build-up of dopamine and corresponding adrenergic substances leads to numerous gastrointestinal and cardiovascular adverse reactions
with levodopa monotherapy.

At therapeutic doses, the decarboxylase inhibitor benserazide does not cross into the brain in appreciable quantities (less than 6% of the plasma concentration). The concomitant administration of benserazide inhibits the peripheral decarboxylation of levodopa (notably in the intestinal mucosa) virtually completely. Consequently, the dose of levodopa required to produce a similar clinical effect can be reduced by ca. 20% compared to the monotherapeutic dose. The gastrointestinal and cardiovascular adverse effects of peripherally accumulated dopamine are also largely avoided.
The benserazide component of the combination may lead to an increase in prolactin concentration, owing to decarboxylase inhibition.

5.2 Pharmacokinetic properties

Absorption
Levodopa is mainly absorbed in the proximal small intestine, independent of the region thereof. Peak plasma concentrations are attained approximately 1 hour after dosing with an immediate-release dosage form. Levodopa peak plasma concentrations and AUC increase in proportion to the dose over the range of 50-200 mg of levodopa.

Food intake reduces the rate and extent of levodopa absorption. Peak levodopa concentrations are reduced by ca. 30%, and delayed two or threefold, after ingestion of a standard meal. The extent of absorption is reduced by ca. 15% after administration with food. The absorption of levodopa is influenced by changes in gastric emptying time.

Distribution
Levodopa crosses the gastric mucosa and the blood-brain barrier (BBB) by means of a saturable transport mechanism. It is not bound to plasma protein. Its volume of distribution is 57 l. The AUC of levodopa in the cerebrospinal fluid is 12% of the value in plasma.

Contrary to levodopa, benserazide does not cross the BBB at therapeutic doses. Benserazide concentrations are highest in the kidneys, lungs, small intestine and liver. Benserazide crosses the placenta.

Biotransformation
Levodopa is mainly metabolised by decarboxylation, O-methylation, transamination and oxidation. The principal metabolic pathway for levodopa is decarboxylation to dopamine by an aromatic amino acid decarboxylase. Its main metabolites are homovanillic acid and dihydroxyphenylacetic acid. Methylation of levodopa to 3-*O*-methyldopa by COMT is a secondary pathway. The elimination half-life of 3-*O*-methyldopa is 15 hours. This metabolite therefore accumulates in patients receiving therapeutic doses of levodopa/benserazide.

The concomitant administration of levodopa and benserazide reduces peripheral decarboxylation. This is manifested in increased plasma levels of amino acids (levodopa, 3-O-methyldopa) and reduced plasma levels of catecholamines (dopamine, noradrenaline) and phenylcarbonyl acids (homovanillic acid, dihydroxyphenylacetic acid).

Benserazide is hydrolysed to trihydroxybenzylhydrazine in the intestinal wall and liver. This metabolite is an active inhibitor of the aromatic amino acid decarboxylase.

Elimination
After inhibition of peripheral levodopa decarboxylation, the elimination half-life of levodopa is ca. 1.5 hours. In elderly parkinsonian patients (65-78 years of age), the elimination half-life is increased by ca. 25%. The clearance of levodopa is 430 ml/min.
Benserazide is almost entirely excreted in the form of metabolites. The metabolites are mainly excreted via the kidneys (64%), and, to a lesser extent, in the faeces (24%).

Bioavailability
The absolute bioavailability of levodopa when administered in combination with benserazide for inhibition of peripheral decarboxylase is 98%, on average (range, 74- 112%).

5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity studies in rats, orally administered levodopa/benserazide caused dose-dependent skeletal changes, originating in the unclosed epiphyseal disks. Bone changes occurred only in growing animals and were caused by benserazide. In dogs, dose-dependent increases in liver enzymes, fatty degeneration of the liver, prolonged prothrombin times and decreased bone marrow haematopoietic tissue were observed.

Genotoxicity
In vitro studies in bacteria and cell cultures show that levodopa and benserazide have a weak genotoxic potential. There was no indication that clinical use would be associated with a genotoxic potential.

Reproductive toxicity
Studies with levodopa/benserazide in rats did not reveal any teratogenic effects. Maternotoxic doses led only to fetal weight loss.

In rabbits, maternotoxic doses of levodopa/benserazide caused embryolethality and increased fetal skeletal abnormalities. These toxic effects were assigned to levodopa, based on previous results with levodopa or benserazide alone, which revealed an increase in skeletal abnormalities and cardiovascular malformations in rabbits given high (maternotoxic) doses of levodopa.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Mannitol
Cellulose, microcrystalline
Povidone K-30
Talc
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Black iron oxide (E172)
Erythrosin (E127)
Indigo carmine (E132)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque HDPE bottle with a white opaque polypropylene screw cap with silica gel desiccant containing 20, 30, 50, 60, 90 & 100 capsules, hard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

TEVA UK Ltd,
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0992

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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