SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Caramet 25 mg/100 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 25 mg carbidopa (as monohydrate) and 100 mg levodopa

For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Orange-brown, round, biconcave prolonged-release tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Idiopathic Parkinson's disease in particular to shorten the 'off' period in patients who have previously been treated with immediate-release levodopa/decarboxylase inhibitors or with just levodopa and who showed motor fluctuations.

Experience with Caramet 25 mg/100 mg Prolonged Release Tablets is limited in patients, who have not been previously treated with levodopa or other anti-Parkinson medications.

4.2 Posology and method of administration

The daily dose of Caramet 25 mg/100 mg Prolonged Release Tablets should be carefully determined. Patients should be closely monitored during the period of dose adjustment, especially with regard to the occurrence or exacerbation of nausea and abnormal involuntary movements such as dyskinesia, chorea and dystonia. In the event of more pronounced gastrointestinal symptoms, particularly if they occur at the start of treatment, antiemetics such as domperidone can occasionally be administered (no metoclopramide-containing products!).

The dosage level and intervals must be determined individually after careful examination by the physician.

Blepharospasm may be an early sign of overdosing.

Most other medicines, used to treat Parkinson's disease, except for levodopa, can be continued during administration of Caramet 25 mg/100 mg Prolonged Release Tablets. However their dosage may need to be adjusted.

Posology

Initial dose

Patients *not previously treated with levodopa*

1 prolonged-release tablet Caramet 25 mg/100 mg Prolonged Release Tablets two to three (or four) times per day. In patients requiring more levodopa the treatment may be started with 1 prolonged-release tablet Caramet 50 mg/200 mg Prolonged Release Tablets twice daily.

The initial daily dose of levodopa must not exceed 600 mg and the doses should be administered with minimum intervals of six hours.

Depending upon the severity of disease, six months of treatment may be required to achieve optimal disease control.

Patients who have previously received levodopa as monotherapy

Levodopa must be discontinued at least 12 hours before therapy with Caramet 25 mg/100 mg Prolonged Release Tablets is started.

- Caramet 25 mg/100 mg Prolonged Release Tablets
  In patients with mild to moderate disease, the recommended initial dose is 2 prolonged-release tablets of Caramet 25 mg/100 mg Prolonged Release Tablets 100 mg/25 mg twice daily.
- Caramet 50 mg/200 mg Prolonged Release Tablets
  In patients with mild to moderate disease, the recommended initial dose is 1 prolonged-release tablet of Caramet 25 mg/100 mg Prolonged Release Tablets 200 mg/50 mg twice daily.

Patients previously treated with immediate-release levodopa/decarboxylase inhibitor

Patients previously treated with non-prolonged-release levodopa/decarboxylase inhibitor products should receive approximately 10% more levodopa than previously at the start of treatment with Caramet 25 mg/100 mg Prolonged Release Tablets. The levodopa dose may need to be up to 30% higher.

Levodopa and decarboxylase inhibitor should be discontinued at least 12 hours before the administration of Caramet 25 mg/100 mg Prolonged Release Tablets.

The dose interval should be prolonged by 30%-50% at intervals in the range of 4 to 12 hours.

If the divided doses are not equal it is recommended to administer the lowest dose at the end of the day.

As described below under 'dose adjustment', the dose should be adjusted in line with the patient's response to treatment.

Guidelines for changing from immediate-release levodopa/decarboxylase inhibitor tablets to Caramet 25 mg/100 mg Prolonged Release Tablets:

	Caramet 25 mg/100 mg Prolonged Release Tablets
immediate-release levodopa/decarboxylase inhibitor tablets	

Daily dose of levodopa (mg)	Daily dose of levodopa (mg)	Number of prolonged-release tablets
100-200	200	1 tablet, twice daily
300-400	400	1 tablet, three to four times daily

Caramet 50 mg/200 mg Prolonged Release Tablets

immediate-release levodopa/decarboxylase inhibitor tablets	Caramet 50 mg/200 mg Prolonged Release Tablets	
Daily dose of levodopa (mg)	Daily dose of levodopa (mg)	Number of prolonged-release tablets
300-400	400	1 tablet, twice daily
500-600	600	1 tablet, three times daily
700-800	800	4 tablets, in three or more divided doses
900-1000	1000	5 tablets, in three or more divided doses
1100-1200	1200	6 tablets, in three or more divided doses
1300-1400	1400	7 tablets, in three or more divided doses
1500-1600	1600	8 tablets, in three or more divided doses

Dose adjustment

Once the dosage has been established, the dose or the dosing interval can be increased or decreased, according to the patient's response to treatment.

Most patients are adequately treated with 400 mg levodopa/100 mg carbidopa to 1600 mg levodopa/400 mg carbidopa per day. The prolonged-release tablets should be taken in single doses at intervals of 4-12 h during the day.

Higher doses (up to 2400 mg levodopa/600 mg carbidopa) and shorter intervals (less than four hours) have been used, but are generally not recommended.

When doses of Caramet 25 mg/100 mg Prolonged Release Tablets are given at intervals of less than four hours or if the divided doses are not equal, it is recommended to administer the lowest dose at the end of the day.

The effect of the first morning dose can be delayed in some patients for up to one hour compared to the usual reaction of the first morning dose of immediate-release levodopa/carbidopa.

Adjustments of the dosage should occur in intervals of at least three days.

Maintenance dose

Because Parkinson's disease is progressive, periodic clinical check-ups are recommended and an adjustment of the dose schedule of Caramet 25 mg/100 mg Prolonged Release Tablets may be needed.

Use of additional anti-Parkinson medications

Anticholinergic agents, dopamine agonists and amantadine can be administered concomitantly with levodopa/carbidopa. It might be necessary to adjust the dose of {Product name} when these medicinal products are added to an ongoing treatment with Caramet 25 mg/100 mg Prolonged Release Tablets.

Interruption of the therapy

Patients should be carefully observed in case of a sudden reduction of the dose or if it is

necessary to discontinue treatment with Caramet 25 mg/100 mg Prolonged Release Tablets, particularly in the patients receiving antipsychotics (see section 4.4).

If anaesthesia with halothane, cyclopropane or other substances that sensitise the heart to sympathomimetic amines is required, the administration of Caramet 25 mg/100 mg Prolonged Release Tablets has to be discontinued (see section 4.5).

Special population
Paediatric population
The safety and efficacy in children under 18 years of age have not been established.

Elderly
There is a wide experience in the use of levodopa/carbidopa in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

Renal and hepatic impairment
No dose adjustment is necessary.

Method of administration
In order to maintain the prolonged-release effect of the medicinal product, the prolonged-release tablets may only be taken whole and may not be divided, chewed or crushed.

Intake of food, especially protein-rich food, may influence the absorption of levodopa. Therefore, the prolonged-release tablets should be taken 30 min before a meal or 90 min after a meal.

4.3 Contraindications

- Hypersensitivity to levodopa, carbidopa or any of the excipients listed in section 6.1.
- Non-selective monoamine oxidase (MAO) inhibitors and selective MAO-A inhibitors. Administration of these MAO inhibitors should be discontinued at least 2 weeks before starting treatment with levodopa/carbidopa. Levodopa/carbidopa may be used concomitantly with the recommended dose of a selective MAO-B inhibitor (e.g., selegiline) (see section 4.5).
- Malignant melanoma. Since levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.
- Narrow-angle glaucoma.

4.4 Special warnings and precautions for use

Levodopa/carbidopa is to be administered only after thorough benefit-risk evaluation:
- to patients with severe cardiovascular or pulmonary disease, bronchial asthma, acute stroke, renal, hepatic or endocrine (e.g. hyperthyroidism, phaeochromocytoma) disease or with a history of peptic ulcer disease or convulsions
- to patients with tachycardia
- to patients with severe disorders of the haematopoietic system
- if administration of a sympathomimetic agent is contraindicated
- to patients with psychiatric diseases with a psychotic component

Care should be exercised when levodopa/carbidopa is administered to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

In the adjustment phases, more frequent monitoring of liver and kidney function and of the blood count is recommended.
If there is a history of myocardial infarction, arrhythmias or coronary ischaemia, circulation and ECG checks should be carried out regularly and frequently, particularly at the start of treatment.
Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

In patients who have previously received levodopa as monotherapy, treatment with levodopa must be discontinued at least 12 hours before starting with the therapy of levodopa/carbidopa.

Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

Levodopa/carbidopa is not recommended for the treatment of drug-induced extrapyramidal reactions or for the treatment of Huntington's chorea.

Abrupt withdrawal
After many years of treatment with products containing levodopa, sudden withdrawal or a very rapid reduction in the dose of Caramet 25 mg/100 mg Prolonged Release Tablets can lead to a malignant levodopa withdrawal syndrome (neuroleptic malignant syndrome with hyperthermia, muscle rigidity, altered mental status and an increase in serum creatine phosphokinase) or akinetic crisis. Both conditions are life-threatening. Levodopa treatment breaks indicated for therapeutic reasons must therefore be carried out only in a hospital setting, especially if the patient is receiving neuroleptics.

Dopamine dysregulation syndrome
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).

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 and 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 Caramet 25 mg/100 mg Prolonged Release Tablets. Review of treatment is recommended if such symptoms develop.

Psychiatric disorders
All patients should be monitored carefully for the development of mental changes and depression with or without suicidal tendencies. Patients with a history of psychoses should be treated with caution.

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 or an episode of sudden sleep onset must refrain from driving or operating machines. A reduction of dosage or termination of therapy may be considered.

Chronic wide-angle glaucoma
Patients with chronic wide-angle glaucoma may be treated cautiously with levodopa/carbidopa provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in eye pressure during the therapy.

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 medicines used to treat Parkinson's disease. Therefore patients and providers are advised to monitor for melanomas on a regular basis when using levodopa/carbidopa. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Laboratory tests
Levodopa and carbidopa have caused abnormalities:

- in the detection of catecholamines, creatinine, uric acid, glucose, alkaline phosphatase, SGOT, SGPT, lactic acid dehydrogenase, bilirubin, blood urea nitrogen
- decreased haemoglobin and haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine
- when a test strip is used to determine ketonuria, levodopa/carbidopa can show a false positive result for urinary ketone bodies. This reaction is not altered by boiling the urine sample.
- false negative results in the examination of glycosuria with the use of glucose oxidase methods.
- and a false positive Coombs test.

Excipient(s)
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged release tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following medicines are administered concomitantly with levodopa/carbidopa:

Antihypertensive agents
Postural hypotension can occur when levodopa/carbidopa is added to the treatment of patients already receiving antihypertensive agents (especially reserpine-containing medicines). Dosage adjustment of the antihypertensive agent may be required when levodopa/carbidopa treatment is added.

Antidepressants
There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants and levodopa/carbidopa (see section 4.3 for patients receiving monoamine oxidase inhibitors).

Anticholinergic agents
Anticholinergics may act synergistically with levodopa, in order to improve tremor. However combined use may exacerbate abnormal involuntary movements. Anticholinergics may decrease the effects of levodopa by delaying its absorption. An adjustment of the dose of levodopa/carbidopa may be needed.

Dopamine-depleting agents (e.g. reserpine, tetrabenazine)
Use of levodopa/carbidopa with dopamine-depleting agents (e.g. reserpine, tetrabenazine) or other agents known to deplete monoamine stores is not recommended.

COMT inhibitors (tolcapone, entacapone)
Concomitant use of COMT (catechol-O-methyltransferase) inhibitors and levodopa/carbidopa can increase the bioavailability of levodopa. The dose of levodopa/carbidopa may need adjusting.

Other anti-Parkinson medications
Anticholinergic agents, dopamine agonists and amantadine can be administered concomitantly with Caramet 25 mg/100 mg Prolonged Release Tablets. It might be necessary to adjust the dose of Caramet 25 mg/100 mg Prolonged Release Tablets when these medications are added to an ongoing treatment of Caramet 25 mg/100 mg Prolonged Release Tablets.

Concomitant use of selegiline and levodopa/carbidopa may be associated with severe postural hypotension (see section 4.3).

Other medicines
Dopamine-D_2-receptor antagonists (e.g. phenothiazines, butyrophenones, risperidone), benzodiazepines and isoniazid can reduce the therapeutic effect of levodopa. The beneficial effects of levodopa in Parkinson's disease may be reduced by phenytoin, papaverine and opioids. Patients taking these medications together with levodopa/carbidopa should be observed carefully for loss of therapeutic response.

Concomitant administration of levodopa/carbidopa with sympathomimetics may potentiate their effects, and the dose of the sympathomimetic agents may need to be reduced.

General anaesthetics
The product must be discontinued at least 8 hours before anaesthesia with halothane, cyclopropane or other substances that sensitise the heart to sympathomimetic amines, unless opioids are used concomitantly.
If the treatment is interrupted temporarily, the usual daily dose should be resumed as soon as the patient is able to take oral medicinal products again.

Pyridoxine (vitamin B_6)
As carbidopa inhibits any attenuation of the effect of levodopa caused by pyridoxine, {Product name} can also be taken by patients who are concurrently receiving pyridoxine (vitamin B_6).

Iron

Concomitant use of ferrous sulphate or ferrous gluconate and levodopa/carbidopa can lead to a reduction in the bioavailability of levodopa/carbidopa.

Protein-rich diet
As levodopa competes with certain amino acids, levodopa absorption may be impaired in some patients who are on a protein rich diet.

Antacids
The effects of administration of antacids and levodopa/carbidopa on the bioavailability of levodopa have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data available on the use of levodopa/carbidopa in pregnant women. The results of animal studies have shown reproduction toxicity (see section 5.3). The potential risk to embryo or the foetus is not known.

Caramet 25 mg/100 mg Prolonged Release Tablets should not be used during pregnancy. Any women of child-bearing potential who is receiving Caramet 25 mg/100 mg Prolonged Release Tablets must practise effective contraception.

Breastfeeding
Significant amounts of levodopa are excreted into the breast milk. While using Caramet 25 mg/100 mg Prolonged Release Tablets women should not breastfeed.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary and certain side effects such as sleepiness and dizziness that have been reported with levodopa/carbidopa may affect some patients' ability to drive or operate machinery.

Patients being treated with levodopa and presenting with somnolence or an episode of sudden sleep onset must be advised 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 also section 4.4).

4.8 Undesirable effects

Summary of the safety profile
During controlled clinical trials in patients with moderate to severe motor fluctuations, levodopa/carbidopa caused no side effects which were unique to the modified release formulations.

The most frequently reported adverse reaction was dyskinesia (a form of abnormal involuntary movements).

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience are listed per System Organ Class and per frequency.

System organ class	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 (frequency cannot be estimated from the available data)
Infections and infestations	Urinary tract infections					
Blood and lymphatic system disorders				leukopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia	agranulocytosis	
Metabolism and nutrition disorders		anorexia	weight loss or gain			
Psychiatric disorders		depression with or without development of suicidal tendencies, psychotic episodes including delusions and paranoid ideation, dementia, euphoria, hallucinations, confusion, dizziness, nightmares, sleepiness[1], insomnia, light-headedness, increased drive	agitation, fear, disorientation	bruxism, increased libido		dopamine dysregulation syndrome
Nervous system disorders		dyskinesia[2], chorea, dystonia,	reduced thinking capacity,	neuroleptic malignant syndrome,		

		extrapyramidal and movement disorders, bradykinesia (on-off episodes)[3], headache, paraesthesia, syncope, bitter taste	ataxia, increased tremor of the hands	activation of a latent Horner's syndrome, convulsions, numbness, trismus		
Eye disorders				blurred vision, blepharospasm, pupil dilation, diplopia, oculogyric crises		
Cardiac disorders		palpitations, cardiac irregularities				
Vascular disorders		orthostatic effects including hypotensive episodes	hypertension	flushing, phlebitis		
Respiratory, thoracic and mediastinal disorders		dyspnoea	hoarseness	abnormal breathing pattern		
Gastrointestinal disorders		constipation, diarrhoea, dyspepsia, nausea, vomiting, dry mouth	abdominal pain, dysphagia, flatulence, sialorrhoea	dark discolouration of the saliva, burning sensation on the tongue, duodenal ulcers, gastrointestinal bleeding, hiccups		
Skin and subcutaneous tissue disorders			urticaria	hair loss, angioedema, dark discolouration of the sweat, increased sweating, pruritus, rash, malignant melanoma (see section 4.4), Henoch-Schoenlein purpura		
Musculoskeletal and connective tissue disorders		muscle cramp				muscle twitching
Renal and urinary disorders			dark discolouration of the urine	urinary incontinence, urinary retention		

Reproductive system and breast disorders				priapism		
General disorders and administration site conditions		chest pain, fatigue, asthenia	gait disturbances, hot flushes, oedema, malaise			
Injury, poisoning and procedural complications			falling			

[1] Levodopa/carbidopa has been associated with somnolence and has been associated very rarely with extreme daytime somnolence and sudden onset of sleep.

[2] During use of levodopa/carbidopa prolonged-release tablets, dyskinesia has been observed more frequently than with use of immediate-release levodopa/carbidopa dosage forms.

[3] An (on-off episodes) bradykinesia may occur some months to years after the beginning of treatment with levodopa and is probably associated to the progression of the disease. Adjustment of the dosage regimen and dosing interval may be required.

Description of selected adverse reactions

Impulse control disorders
Pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating or compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including levodopa/carbidopa (see section 4.4 “Special warnings and precautions for use”).

Dopamine dysregulation syndrome
Dopamine dysregulation syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/carbidopa. 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).

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

4.9 Overdose

The treatment of an acute overdose of Caramet 25 mg/100 mg Prolonged Release Tablets is in general the same as that of an acute overdose of levodopa. However, pyridoxine has no effect on the reversal of the action of Caramet 25 mg/100 mg Prolonged Release Tablets. Electrocardiographic monitoring should be used and the patient observed carefully for the development of cardiac arrhythmias. If necessary an appropriate antiarrhythmic therapy should be given (e.g. β-receptor inhibitors).

A specific antidote does not exist.

The possibility that the patient may have taken other medicinal products together with Caramet 25 mg/100 mg Prolonged Release Tablets should be considered. To date experience with dialysis has not been reported. Therefore, its value in the treatment of overdose is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: dopaminergic agents; levodopa and decarboxylase inhibitor
ATC-Code: N04BA02

Caramet 25 mg/100 mg Prolonged Release Tablets is a combination of carbidopa, an inhibitor of aromatic amino acid decarboxylase, and levodopa, the metabolic precursor of dopamine, in the form of a tablet with a polymer-based delayed release of the active agent for use in the treatment of Parkinson's disease.
Levodopa/carbidopa prolonged-release tablets are particularly useful in the reduction of the "off" period in patients previously treated with the immediate-release levodopa/decarboxylase inhibitor combination who have had dyskinesia and motor fluctuations.

Patients with Parkinson's disease who were treated with preparations that contained levodopa, can develop motor fluctuations which are characterized by the wearing off effect of a dose, dyskinesia in the peak dose and akinesia. The advanced form of motor fluctuations ("on-off" phenomenon) is characterised by unpredictable fluctuations from mobility to immobility. Although the causes of the motor fluctuations are not completely clear, it has been shown that they can be reduced by treatment schedules that provide a stable plasma concentration of levodopa.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not pass the blood/brain barrier, inhibits only the extra-cerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine. Therefore it is normally not necessary to administer high doses of levodopa at frequent intervals.

Gastro-intestinal and cardio-vascular side-effects, in particular those which can be attributed to the dopamine formed in the extra-cerebral tissues, are avoided totally or partially by the reduced dose.

During clinical trials patients with motor fluctuations experienced a shorter "off" period with levodopa and carbidopa in retard form in comparison with an immediate-release tablet of a combination of levodopa and carbidopa. The reduction of the "off" time is rather small (about 10%) and the incidence of dyskinesia was slightly increased after administration of levodopa/carbidopa prolonged release tablet compared to treatment with an immediate-release tablet of a combination of levodopa and carbidopa. In patients without motor fluctuations levodopa/carbidopa prolonged-release tablet provided, under controlled circumstances, the same therapeutic advantage in less frequent doses than the immediate-release tablet with a combination of levodopa and carbidopa. Improvement of other symptoms of Parkinson's Disease did not generally take place.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of levodopa after administration of levodopa/carbidopa 200 mg/50 mg in prolonged release form compared to an immediate release levodopa/carbidopa 200 mg/50 mg tablet has been studied in young healthy volunteers. After administration of levodopa/carbidopa 200 mg/50 mg prolonged release tablet it took approximately two hours before maximal levodopa plasma levels were reached in comparison to 0.75 hours for the immediate-release tablet. The mean maximal levodopa plasma levels were reduced 60% in levodopa/carbidopa 200 mg/50 mg prolonged release tablets compared in immediate-release tablets. The absorption of levodopa after the administration of levodopa/carbidopa 200 mg/50 mg prolonged release tablets occurred continuously for four to six hours. In these studies the levodopa plasma concentrations fluctuated within closer margins than with the immediate-release tablet of levodopa and carbidopa. As the bio-availability of levodopa from levodopa/carbidopa 200 mg/50 mg prolonged release tablet in comparison to an immediate-release tablet with a combination of levodopa and carbidopa is approximately 70%, the daily dose of levodopa in the modified release formulation should as a rule be higher than that of the immediate-release product.

The mean maximal plasma concentration of levodopa after the administration of a single dose levodopa/carbidopa 100 mg/25 mg prolonged release tablet was approximately 70% of levodopa/carbidopa 200 mg/50 mg prolonged release tablet.

The mean time to reach the maximal plasma concentrations was reduced a little with levodopa/carbidopa 100 mg/25 mg prolonged release tablet over levodopa/carbidopa 200 mg/50 mg prolonged release tablet.

The pharmacokinetics of levodopa after administration of levodopa/carbidopa prolonged release tablet was also studied in patients with Parkinson’s Disease. Regular twice daily administering of levodopa/carbidopa 100/25 mg prolonged release tablet (varying from 50 mg carbidopa and 200 mg levodopa to 150 mg carbidopa and 600 mg levodopa) for three months showed no accumulation of levodopa in the plasma.

Intake of food had no influence on the absorption of levodopa. With regard to carbidopa the simultaneous intake of food resulted in a 50% AUC reduction and a 40% Cmax reduction. The reduced plasma levels of carbidopa have no clinical relevance.

Distribution

Levodopa is widely distributed to most body tissues, but not to the central nervous because of extensive metabolism in the periphery. Levodopa is not bound to proteins.

Levodopa crosses the blood-brain barrier by an active but saturable transport system for large neutral amino acids.

Carbidopa does not cross the blood brain barrier. Both levodopa and carbidopa cross the placenta and are excreted in breast milk.

Biotransformation and elimination

In the presence of carbidopa, levodopa is mainly metabolised to amino acids and, to a less extent, to catecholamine derivates. All metabolites are excreted renally.

Following an oral dose approximately 50% is recorded in the urine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies both levodopa and the combination of levodopa/carbidopa have caused visceral and skeletal malformations in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Fumaric acid
Hypromellose
Sodium stearyl fumarate
Silica colloidal anhydrous
Quinoline yellow (E104)

Coating:

Hypromellose
Iron oxide yellow (E172)
Iron oxide red (E172)
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blister pack with 20, 30, 50, 60 and 100 prolonged-release tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0924

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/10/2012

10 DATE OF REVISION OF THE TEXT

27/09/2023