SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lecado 100/25 mg Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 100 mg levodopa and 20 mg carbidopa (as carbidopa monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lecado 100/25 mg modified-release tablets
Orange-brown, round tablets

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. The experience with Lecado is limited in patients, who have not been previously treated with levodopa.

4.2 Posology and method of administration

Posology

The daily dose of levodopa/carbidopa should be carefully determined. Patients should be monitored closely 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. Blepharospasm could be an early sign of overdosing.

- Starting dose

Patients who have never before received Levodopa therapy

Lecado 100/25 mg is designed for use in patients, who have not previously had levodopa treatment or to aid titration in patients who receive Lecado 200/50 mg. The recommended starting dose is one tablet of Lecado 100/25 mg two times per day. In patients who need more levodopa a daily dose of three to four tablets of Lecado 100/25 mg is usually well tolerated.

For Lecado 200/50 mg the recommended starting dose is one tablet two times per day.

The starting dose should not be higher than 600 mg levodopa per day and the doses should be administered with minimum intervals of six hours.

Dose adjustments should occur with intervals of at least two to four days.

Depending of the severity of the disease, six months of treatment may be required to achieve optimal disease control.
A guide to substitution for patients who are treated with the immediate-release combination of levodopa and decarboxylase inhibitor
Transferring to Lecado 100/25 mg should initially occur in a dose that supplies at most about 10% more levodopa per day when higher doses are indicated (more than 900 mg daily). Levodopa and decarboxylase inhibitor should be discontinued at least 12 hours before the administration of Lecado. The dose interval should be prolonged by 30 % to 50% at intervals of ranging from 4 – 12 hours. If the divided doses are not equal it is recommended to administer the lowest dose at the end of the day. The dose should be adjusted depending on the clinical reaction, as indicated below in Dose Adjustment. It could be that doses which supply maximally 30% more levodopa per day are necessary.

A guide for the substitution of Lecado prolonged-release treatment for immediate-release levodopa/carbidopa combinations is shown in the table below:

Levodopa/carbidopa	Lecado 100/25 mg	
Daily dose Levodopa (mg)	Daily dose Levodopa (mg)	Dose schedule
100-200	200	1 tablet, twice daily
300-400	400	4 tablets divided in 3 or more doses

For higher doses Lecado200/50 mg is available.

Levodopa/carbidopa	Lecado 200/50 mg	
Daily dose Levodopa (mg)	Daily dose Levodopa (mg)	Dose schedule
300-400	400	1 tablet, twice daily
500-600	600	1 tablet, 3 times per day
700-800	800	4 tablets*
900-1000	1000	5 tablets*
1100-1200	1200	6 tablets*
1300-1400	1400	7 tablets*
1500-1600	1600	8 tablets*

*divided in 3 or more doses

Patients who are currently treated with just levodopa alone

Levodopa must be discontinued at least twelve hours before therapy with Lecado tablet is started.
In patients with a mild to moderate form of the disease the recommended starting dose is 200 mg levodopa / 50 mg carbidopa twice daily.

- Dose Adjustment

After the treatment is established the doses and the dose frequency can be increased or decreased depending on the therapeutic response. Most patients are adequately treated with 400 mg levodopa / 100 mg carbidopa to 1600 mg levodopa / 400 mg carbidopa per day, administered in divided doses at intervals ranging from four to twelve hours during the waking 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 Lecado 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 Lecado may be needed.

- Addition of other anti-Parkinson medications

Anti-cholinergics, dopamine agonists and amantadine can be administered concomitantly with Lecado. It might be necessary to adjust the dose of Lecado when these medications are added to an ongoing treatment of Lecado.

- 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 Lecado, particularly in the patient who is receiving anti-psychotics. (see section 4.4).

Sudden withdrawal of levodopa therapy should be avoided wherever possible.

- *Paediatric population*

  The safety and effectiveness of Lecado in infants and children has not been established, and its use in patients below the age of 18 is not recommended.

- *Use in the elderly*

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

- *Use in renal/hepatic impairment*
  No dose adjustment is necessary.

Method of administration
The pharmacokinetic properties of the modified-release tablets may be altered if the tablets are broken or chewed. Therefore the tablets must be swallowed whole.

Most other medicines, used to treat Parkinson´s Disease, except for levodopa, can be continued during administration of Lecado. However their dosage may need to be adjusted.
Sudden withdrawal of levodopa therapy should be avoided wherever possible.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, Lecado can be administered to patients who receive supplemental pyridoxine (Vitamin B6).

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4.3 Contraindications

Lecado should not be given when administration of a sympathomimetic amine is contraindicated.

Non-selective mono-amino-oxydase (MAO) inhibitors and selective MAO type A inhibitors are contraindicated for concomitant use with Lecado. The administration of these inhibitors should be discontinued at least two weeks before starting the treatment with Lecado. Lecado can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO type B (for instance selegiline-HCl) (see section 4.5).

Lecado is contraindicated in:
- patients with a hypersensitivity to levodopa, carbidopa or any of the excipients
- patients with narrow-angle glaucoma
- patients with severe heart failure
- severe cardiac arrhythmia
- acute stroke
- patients with severe phychoses.

Since levodopa may activate a malignant melanoma, levodopa/carbidopa should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

4.4 Special warnings and precautions for use

In patients who are treated with just levodopa**,** treatment should have been discontinued for at 12 hours before starting with the therapy of Lecado.

Based on the pharmacokinetic profile of Lecado the onset of effect in patients with early morning dyskinesia may be slower than with immediate-release levodopa/ carbidopa. The incidence of dyskinesia is greater during treatment with Lecado in patients with an advanced stage of motor fluctuations than it is with an immediate-release tablet with a combination levodopa/carbidopa (16.5% versus 12.2%).

Dyskinesia can occur in patients who previously were treated with just levodopa, because carbidopa makes it possible for more levodopa to reach the brain, which causes more dopamine to be formed. The occurrence of dyskinesia may make it necessary to reduce the dose (see section 4.8).

Lecado is not recommended for the treatment of drug-induced extrapyramidal reactions or for the treatment of Huntingdon's chorea.

Lecado should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease or with a history of peptic ulcer disease, haematemesis or of convulsions.

Care should be exercised in administering Lecado to patients with a history of myocardial infarction, who have residual atrial, nodal or ventricular arrhythmia. In such patients cardiac function should be monitored with particular care during the period of initial dosage administration and titration.

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.

Lecado can, just like levodopa, cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone or with carbidopa-levodopa combination should be observed carefully when Lecado is substituted. It is suspected that these reactions are the result of the increased dopamine in the brain after administration of levodopa, and the use of Lecado can cause a recurrence. It may be necessary to reduce the dose. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychosis should be treated with caution.

Lecado should be discontinued when there is deterioration of any pre-exiting psychotic condition.

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

If general anaesthesia is required, the administration of Lecado can be continued as long as the patient is allowed to take oral medications. In case of a temporary interruption of the therapy, the usual dose can be administered as soon as the patient is able to take the oral medications

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 medicinal products used to treat Parkinson's disease.

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

Laboratory tests
Carbidopa/levodopa preparations have given rise to abnormalities in several laboratory tests and these can also occur with Lecado. These include elevations of liver function tests, such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic acid dehydrogenase, bilirubin, blood urea nitrogen, creatinine, uric acid and a positive Coombs test.

Decreased haemoglobin and haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have also been reported with Lecado.

When a test strip is used to determine ketonuria, carbidopa/levodopa preparations can show a false positive result for urinary ketone bodies. This reaction is not altered by boiling the urine sample. False negative results can also occur in the examination of glycosuria with the use of glucose oxidase methods.

Dopamine Dysregulation Syndrome (DDS)
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, hypersexuality, compulsive spending or buying, binge eating and compulsive

eatingcan occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa, including Lecado 200/50 mg. Review of treatment is recommended if such symptoms develop.

A symptom complex resembling the neuroleptic malignant syndrome, including muscular rigidity, increased body temperature, mental changes and increased serum creatine phosphokinase, has been reported when anti Parkinsonian medication was withdrawn abruptly. Therefore patients should be carefully observed when the dose of carbidopa/levodopa combinations is abruptly reduced or discontinued, especially if the patient is receiving anti-psychotics.

Caution should be exercised with concomitant administration of psychoactive drugs and levodopa/carbidopa (see section 4.5).

As with levodopa, periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

(see also section 4.8).

Paediatric population
The safety and efficacy of Lecado has not been determined in infants and children and use in patients under the age of eighteen is not advised.

Lecado contains 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 is needed in concomitant administration of Lecado with the following medicines:

Antihypertensive agents
Symptomatic postural hypotension has occurred when levodopa/carbidopa is added to the treatment of patients receiving some antihypertensive medicinal products. Therefore, when therapy with levodopa/carbidopa is started, dose adjustment of the antihypertensive medicinal product may be required.

Anti- depressants
There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic anti-depressants and carbidopa/levodopa preparations. (see section 4.3 for patients receiving mono-amine oxidase inhibitors).

Anti-cholinergics

Anti-cholinergics may act synergistically with levodopa to decrease 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 Lecado may be needed.

COMT inhibitors (tolcapone, entacapone)
Concomitant use of COMT (Catechol-O-Methyl Transferase) inhibitors and Lecado can increase the bioavailability of levodopa. The dose of Lecado may need adjusting.

Symptomimetics
Sympathomimetics may increase cardiovascular side events related to levodopa.

Antacids
The effect of administration of antacids and Lecado on the bioavailability of levodopa has not been studied.

Iron
Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulfate or ferrous gluconate.

Paediatric population
Interaction studies have only been performed in adults.

Other medicines
Dopamine-D2-receptor antagonists (for instance phenothiazines, butyrophenons, risperidone), benzodiazepines and isoniazide can reduce the therapeutic effect of levodopa. The beneficial effects of levodopa in Parkinson's disease may be reduced by phenytoin and papaverine. Patients taking these medications together with Lecado, should be observed carefully for loss of therapeutic response.

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

Concomitant use of selegiline and levodopa-carbidopa may be associated with severe orthostatic hypotension not attributable to levodopa/carbidopa alone. (See section 4.3)

Since levodopa competes with certain amino acids, the absorption of levodopa may be impaired in some patients on a high protein diet.

Amantadine has a synergistic effect with levodopa and may increase levodopa-related side events. An adjustment of the dose of Lecado may be needed.

Metoclopramide increases gastric emptying and may increase the

bioavailability of Lecado.

Laboratory tests
See section 4.4

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient data on the use of levodopa/carbidopa in pregnant women. The results of animal studies have shown reproduction toxicity (see section 5.3). The potential human risk to the embryo or the foetus is not known. Lecado should not be used during pregnancy. Any woman of childbearing potential who is receiving Lecado must practise effective contraception.

Breast-feeding
Significant amounts of levodopa and carbidopa are excreted into the breast milk. Levodopa inhibits prolactin release and hence lactation. Women should avoid breast-feeding during treatment with Lecado.

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

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary. Certain side effects such as sleepiness and dizziness may influence the ability to drive or use machines.

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

Side effects that occur frequently in patients receiving levodopa/carbidopa are those due to the central neuropharmacologic activity of dopamine. These reactions usually can be diminished by dose reduction. The most common side effects are dyskinesias, including choreiform, dystonic, and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dose reduction.

During controlled clinical studies in patients with moderate to severe motor fluctuations Lecado caused no side effects which were unique to the modified release formulation.

Infections and Infestations
Very common (≥ 1/10): Urinary tract infections

Blood and lymphatic system disorders
Rare (≥ 1/10,000 to < 1/1,000): Leukopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia
Very rare (< 1/10,000): Agranulocytosis

Metabolism and nutrition disorders
Common (≥ 1/100 to < 1/10): Anorexia
Uncommon (≥ 1/1,000 to < 1/100): Loss of weight, increased weight

Psychiatric disorders
Common (≥ 1/100 to < 1/10): Hallucinations, confusion, dizziness, nightmares, sleepiness, fatigue, sleeplessness, depression with very rare suicide attempts, euphoria, psychotic episodes, feeling of stimulation

Rare (≥ 1/10,000 to < 1/1,000): Agitation, fear, reduced thinking capacity, disorientation, headache, increased libido, numbness and convulsions

Unknown frequency:
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 Lecado.(see section 4.4).

Psychiatric disorders: dementia

Dopamine dysregulation syndrome: 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).

Nervous system disorders
Common (≥ 1/100 to < 1/10): Dyskinesia (a higher frequency of dyskinesia was seen with Lecado than with the immediate-release formulation of Levodopa/Carbidopa), chorea, dystonia, extrapyramidal and movement disorders, the “on-off”-appearance

Bradykinesia (on-off episodes) may appear some months to years after the beginning of treatment with levodopa and is probably related to the progression of the disease. The adaptation of dose schedule and dose intervals may be required.

Uncommon (≥ 1/1,000 to < 1/100): Ataxia, increased tremor of the hands
Rare (≥ 1/10,000 to < 1/1,000): Neuroleptic Malignant Syndrome (see 4.4.), paraesthesia, falling, walking defects, trismus

Levodopa/carbidopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Eye disorders
Rare (≥ 1/10,000 to < 1/1,000): Hazy vision, blepharospasm, activation of a latent Horner's syndrome, double vision, dilated pupils and oculogyric crises

Blepharospasm can be an early sign of overdosage.

Cardiac disorders
Common (≥ 1/100 to < 1/10): Palpitations, irregular heartbeat

Vascular disorders
Common (≥ 1/100 to < 1/10): Orthostatic hypotension, inclination to faint, syncope
Uncommon (≥ 1/1,000 to < 1/100): Hypertension
Rare (≥ 1/10,000 to < 1/1,000): Phlebitis

Respiratory, thoracic and mediastinal disorders
Uncommon (≥ 1/1,000 to < 1/100): Hoarseness, chest pain
Rare (≥ 1/10,000 to < 1/1,000): Dyspnoea, abnormal breathing pattern

Gastrointestinal disorders
Common (≥1/100 to < 1/10): Nausea, vomiting, dry mouth, bitter taste
Uncommon (≥1/1,000 to <1/100): Constipation, diarrhoea, sialorrhoea, dysphagia, flatulence
Rare (≥1/10,000 to <1/1,000): Dyspepsia, gastro-intestinal pain, dark saliva, bruxism, hiccups, gastrointestinal bleeding, burning sensation of the tongue, duodenal ulceration

Skin and subcutaneous tissue disorders
Uncommon (≥ 1/1,000 to < 1/100): Oedema
Rare (≥ 1/10,000 to < 1/1,000): Angioedema, urticaria, pruritus, facial redness, hair loss, exanthema, increased perspiration, dark perspiration fluid and Schönlein-Henoch purpura
Unknown frequency*:* Malignant melanoma (see section 4.3)

Musculoskeletal, connective tissue and bone disorders
Uncommon (≥ 1/1,000 to < 1/100): Muscle spasms

Renal and urinary disorders
Uncommon (≥ 1/1,000 to < 1/100): Dark urine

Rare (≥ 1/10,000 to < 1/1,000): Urinary retention, urinary incontinence, priapism

General disorders and administration site conditions
Uncommon (≥ 1/1,000 to < 1/100): Weakness, malaise, flare ups

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: 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 Lecado 100/25 mg 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 Lecado. 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. The possibility that the patient took other medications together with Lecado 100/25 mg should be taken into consideration. To date experiences with dialysis have not been reported, therefore its value in the treatment of overdose is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: levodopa: dopaminergics; carbidopa: dopadecarboxylase inhibitor
ATC code: N04BA02
Mechanism of action
Lecado is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in the form of a prolonged-release tablet on a polymer base for use in the treatment of Parkinson's Disease.
Lecado is 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.

Pharmacodynamic effects
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 characterized 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.

Clinical efficacy and safety
During clinical trials patients with motor fluctuations experienced a shorter "off" period with levodopa and carbidopa in modified 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 compared to treatment with an immediate-release tablet of a combination of levodopa and carbidopa. In patients without motor fluctuations levodopa+carbidopa prolonged-release 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+50 mg in prolonged-release form compared to an immediate release Levodopa+Carbidopa 200+50 mg tablet has been studied in young healthy volunteers. After administration of Levodopa+Carbidopa 200+50 mg prolonged-release 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+50 mg prolonged-release compared to immediate-release tablets. The absorption of levodopa after the administration of Levodopa+Carbidopa 200+50 mg prolonged-release 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+50 mg prolonged-release 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+25 mg prolonged release was approximately 70% of Levodopa+Carbidopa 200+50 mg prolonged release.
The mean time to reach the maximal plasma concentrations was reduced a little with Levodopa+Carbidopa 100+25 mg prolonged release over Levodopa+Carbidopa 200+50 mg prolonged release.

The pharmacokinetics of levodopa after administration of Levodopa+Carbidopa retard was also studied in patients with Parkinson´s Disease. Regular twice daily administering of Levodopa+Carbidopa 100+25 mg prolonged release (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% C-max 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 system 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.

Metabolism 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

Animal studies with regard to the pharmacological safety and toxicity after repeated administration, mutagenicity studies and carcinogenicity investigations showed no particular risk for humans. In reproductive toxicity studies both levodopa and the combination of carbidopa/levodopa have caused visceral and skeletal malformations in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose

Colloidal anhydrous silica

Fumaric acid

Sodium stearyl fumarate

Macrogol 6000

Quinoline yellow (E104)

Iron oxide yellow (E172)

Iron oxide red (E172)

Titanium dioxide (E171)

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 storage conditions.

6.5 Nature and contents of container

Blister packs (Aluminium/Aluminium)

30, 50, 60 and 100 modified-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0856

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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