Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Apodespan PR 50 mg/200 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 50 mg of Carbidopa and 200 mg of Levodopa
Excipient with known effect: Lactose monohydrate (24.00 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged Release Tablet

Peach to light peach colored with mosaic appearance, oval shaped, biconvex tablets of approximately 13.0 mm in length and approximately 7.0 mm in width debossed with ‘L200’on one side and plain on other side.

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 who showed motor fluctuations.

Experience with Apodespan PR is limited in patients, who have not been previously treated with levodopa.

4.2 Posology and method of administration

The daily dosage of Apodespan PR 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.

The pharmacokinetic properties of the prolonged-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 Apodespan PR. 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, Apodespan PR can be administered to patients who receive supplemental pyridoxine (vitamin B_6).

Starting dose

Patients who have never before received Levodopa therapy
* For doses not achievable with Carbidopa and Levodopa Accord 50 mg/200 mg prolonged release Tablets, other brands of carbidopa and levodopa prolonged-release tablets are available and can be used.

Carbidopa and Levodopa 25 mg/100 mg prolonged release tablets* is recommended for use in patients, who have not previously had levodopa treatment or to aid titration in patients who receive Carbidopa and Levodopa Accord 50 mg/200 mg prolonged release Tablets. The recommended starting dose is one tablet 25/100 mg two times per day.

In patients who need more levodopa a daily dose of three to four tablets of Carbidopa and Levodopa 25 mg/100 mg

prolonged release tablets* is usually well tolerated. For Carbidopa and Levodopa Accord 50 mg/200 mg prolonged release Tablets the recommended starting dose is two times per day one tablet.

The starting dose should not be higher than 600 mg levodopa per day and the doses should be administered with minimum intervals 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 Apodespan PR 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 Apodespan PR. 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 Apodespan PR treatment for immediate-release levodopa/carbidopa combinations is shown in the table below:

Levodopa/carbidopa	Carbidopa and Levodopa 25 mg/100 mg prolonged release Tablets*	
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 doses not achievable with Carbidopa and Levodopa Accord 50 mg/200 mg prolonged release Tablets, other brands of carbidopa and levodopa prolonged-release tablets are available and can be used.		

Levodopa/carbidopa	**Apodespan PR 50 mg/200 mg Prolonged release tablets**	
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
Levodopa must be discontinued at least twelve hours before therapy with Apodespan PR is started. In patients with mild to moderate form of the disease, the recommended starting dose is Carbidopa and Levodopa Accord 50 mg/200 mg prolonged release Tablets 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 Apodespan PR 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 Apodespan PR may be needed.

Addition of other antiparkinson medication
Anticholinergic agents, dopamine agonists and amantadine can be administered concomitantly with Apodespan PR or Carbidopa. It might be necessary to adjust the dose Apodespan PR when these medications are added to an ongoing treatment of Apodespan PR.

Interruption of therapy
Patients should be carefully observed in case of a sudden reduction of the dose or if it is necessary to discontinue treatment with Apodespan PR, particularly in the patient who is receiving antipsychotics (see 4.4 'Special warnings and precautions for use').
If an anaesthetic is necessary, the administration of Apodespan PR 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.

Use in Children
The safety in patients under 18 years of age 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
Renal impairment
No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, therefore Levodopa/Carbidopa should be administered cautiously to patients with severe renal impairment including those receiving dialysis therapy. The dose should be titrated individually.

Hepatic impairment
Levodopa/Carbidopa is contraindicated in patients with severe hepatic impairment (see section 4.3). For patients with mild to moderate hepatic impairment caution is advised. The dose should be titrated individually.

4.3 Contraindications

Apodespan PR 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

Apodespan PR should not be given when administration of a sympathomimetics is contraindicated.

Non-selective mono-amine oxydase (MAO) inhibitors and selective MAO type A inhibitors are contraindicated for concomitant use with Apodespan PR. The administration of these inhibitors should have been discontinued at least two weeks before starting the treatment with Apodespan PR. Apodespan PR can be taken concomitantly with the recommended dose of an MAO inhibitors which is selective for MAO type B (for instance selegiline-HCl). (See 4.5 'Interactions with other medicinal products and other forms of interaction').

In conditions where adrenergic drugs are contraindicated, e.g. severe liver disease, pheochromocytoma, hyperthyroidism, Cushing's syndrome, severe cardiovascular diseases. Because levodopa may activate a malignant melanoma, Apodespan PR 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 Apodespan PR

Based on the pharmacokinetic profile of Apodespan PR 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 Apodespan PR retard 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).

Apodespan PR 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 Apodespan PR 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 Apodespan PR 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.

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

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.

Apodespan PR 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 (See also section 4.3).

Apodespan PR should be administered cautiously to patients who have had a recent 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.

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

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 antiparkinsonian 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.

The use of Apodespan PR is not advised during treatment for pharmacogenic extra-pyramidal reactions or Huntington´s chorea.
Periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

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

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 Apodespan PR. Review of treatment is recommended if such symptoms develop.

Patients with Parkinson’s disease show a possible increased risk of melanoma but no confirmed association with levodopa therapy has been established.
Therefore caution should be exercised during treatment.

Laboratory Tests
Carbidopa/levodopa preparations have given rise to abnormalities in several laboratory tests and these can also occur with Apodespan PR. 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 positive Coombs test.

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

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.

Lactose: Apodespan PR Prolonged-Release Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is needed in concomitant administration of Apodespan PR

Anti-hypertensives
Symptomatic orthostatic dysregulation has occurred when levodopa is added with a decarboxylase inhibitor to certain antihypertensives. Dose adjustment of antihypertensives may be necessary during the titration phase of treatment with

Apodespan PR.

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

Anticholinergics
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 Levodopa/Carbidopa may be needed.

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 Apodespan PR should be observed carefully for loss of therapeutic response.

Concomitant use of selegiline and levodopa-carbidopa may be associated with severe orthostatic hypotension (see section 4.3 'Contraindications').

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

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

Metoclopramide increases gastric emptying and may increase the bioavailability of Apodespan PR.

Sympathomimetics may increase cardiovascular side events related to levodopa

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

As levodopa competes with certain amino acids, the absorption of levodopa can be impaired in some patients who are on a protein rich diet.

Concurrent administration of iron sulphate and levodopa/carbidopa reduces the bioavailability of levodopa with approximately 50 %, most likely because of chelate formation. The bioavailability of carbidopa is also decreased by approximately 75 %. Products containing iron sulphate and levodopa/carbidopa should be administered separately with the longest possible time interval.

The effect of administration of antacids and Levodopa/Carbidopa retard on the bioavailability of levodopa has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy
They are insufficient data on the use of levodopa/carbidopa in pregnant women. The results of animal studies have shown reproduction toxicity (See 5.3 'Preclinical Safety Data'). The potential human risk to the embryo or the foetus is not known.

Apodespan PR should not be used during pregnancy. Any woman of childbearing potential who is receiving Apodespan PR must practise effective contraception.

Lactation

It is not known whether carbidopa is excreted in human milk. Carbidopa was excreted in small amounts in milk of rats. Levodopa is secreted in breast milk. While using Apodespan PR women should not breast feed.
Carbidopa and levodopa are known to suppress prolactin production.

Fertility
There are no data regarding potential effects of levodopa and carbidopa on fertility.

4.7 Effects on ability to drive and use machines

There are no known data on the effect of this product on the ability to drive. 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 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 'Special warnings and precautions for use')

4.8 Undesirable effects

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

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, dementia, feeling of stimulation, dream abnormalities
Rare (≥ 1/10,000 to < 1/1,000): Agitation, fear, reduced thinking capacity, disorientation, headache, increased libido, numbness and convulsions, psychotic episodes including delusions and paranoid ideation

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 Apodespan PR.(see section 4.4 ‘Special warning and precautions for use).

Nervous system disorders
Common (≥ 1/100 to < 1/10): Dyskinesia (a higher frequency of dyskinesia was seen with Apodespan PR 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): Malignant neuroleptic syndrome, 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.

Not known: Muscle twitching

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, gastrointestinal 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

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
Asthenia
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The treatment of an acute overdose with Apodespan PR 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 Apodespan PR Electrocardiographic monitoring should be used and the 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 Apodespan PR should be taken into consideration.

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

Pharmaco-therapeutic group: *levodopa:* dopaminergics; *carbidopa:* dopadecarboxylase inhibitor
ATC code: N04B A02

Apodespan PR is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in the form of prolonged-release tablet on apolymer base for use in the treatment of Parkinson's disease.

Apodespan PR are particularly useful in the reduction of the 'off'' period in patients treated previously 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 characterised 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 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 cross 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 dopamine formed in 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 carbidopa and levodopa 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 carbidopa and levodopa prolonged release Tablets compared to to treatment with an immediate-release tablet of a combination of levodopa and carbidopa. In patients without motor fluctuations, Carbidopa and Levodopa Prolonged-Release Tablets under controlled circumstances, the same therapeutic advantage in less frequent doses than 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 retard 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 retard 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 retard compared in immediate-release tablets. The absorption of levodopa after the administration of levodopa+carbidopa 200+50 mg retard 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 retard 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.

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 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 aminoacids 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

Cellulose, microcrystalline
Lactose monohydrate
Ferric oxide red (E172)
Ferric oxide yellow (E172)
Hypromellose K4M
Hypromellose E5
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years
In-use shelf life after first opening: 2 months

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Apodespan PR Prolonged-Release Tablets are available in the following pack sizes:
Blister(s) in outer carton:
Alu/Alu blister of 10, 20, 30, 49, 50, 56, 60, 84, 98, 100, 196, 200 and/or 300 Tablets.

HDPE bottle inserted with cotton and desiccant, fitted with PPCRC closure. Each bottle contains 30, 56, 84 and/or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1390/042/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st February 2013

10 DATE OF REVISION OF THE TEXT

November 2014