Public Assessment Report

CARLEPONE

INFORMASI PRODUK

Nama obat	:	CARLEPONE
No. Aju	:	EREG10006112100108
Zat aktif	:	Carbidopa 50 mg, Levodopa 200 mg, Entecapone 200 mg
Bentuk sediaan	:	Tablet salut selaput
Kemasan	:	Dus, 3 blister @ 10 tablet salut selaput
Pendaftar	:	PT. Soho Industri Farmas
Produsen	:	Macleods Pharmaceuticals, India
Kategori Registrasi	:	Obat baru yang sudah terdaftar dengan kekuatan baru
Indikasi yang diajukan:	:	*Carbidopa + Levodopa + Entacapone Tablets is indicated for the treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.*
Posologi yang diajukan	:	*The optimum daily dosage must be determined by careful titration of levodopa in each patient. The daily dose should preferably be optimised using one of the four available tablet strengths (18.75/75/200mg, 25/100/200 mg, 31.25/125/200 mg or 50/200/200 mg carbidopa/ levodopa/entacapone).* *Patients should be instructed to take only one Carbidopa + Levodopa + Entacapone tablet per dose administration. Patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting. While the experience with total daily dosage greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2000 mg and therefore the maximum Carbidopa + Levodopa + Entacapone dose, for the Carbidopa + Levodopa + Entacapone strengths of 18.75/75/200 mg, 25/100/200 mg, 31.25/125/200 mg is 10 tablets per day. Ten (10) tablets of Levodopa+Carbidopa+Entecapone 150/37.5/200 mg equal 375 mg of Carbidopa a day. Therefore, using maximum recommended daily dose of 375 mg of carbidopa, the maximum daily dose of Carbidopa + Levodopa + Entacapone tablet 50/200/200 mg is 7 tablets per day.* *The maximum total daily levodopa dose administered in the form of Carbidopa + Levodopa + Entacapone tablet should not exceed 1500 mg.* *Starting Carbidopa + Levodopa + Entacapone tablet therapy* *Switching from levodopa/ DDC inhibitor (carbidopa or benserazide) preparations and entacapone to Carbidopa + Levodopa + Entacapone tablet.* *Usually Carbidopa + Levodopa + Entacapone tablet is intended for use in patients already receiving treatment with corresponding doses of standard-release levodopa/DDC inhibitor and entacapone.*

As with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet.

Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

a) *Patients who are currently receiving treatment with entacapone and standard-release levodopa/carbidopa in doses equal to Carbidopa + Levodopa + Entacapone tablet strengths can be directly switched to the corresponding Carbidopa + Levodopa + Entacapone tablet. For example:*

Levodopa/ Carbidopa	*Entacapone*	*Equivalent Carbidopa + Levodopa + Entacapone tablet*
100/25 mg	*200 mg*	*25/100/200 mg*

b) *When initiating Carbidopa + Levodopa + Entacapone tablet therapy in patients currently receiving treatment with entacapone and levodopa/carbidopa in doses not equal to the available Carbidopa + Levodopa + Entacapone tablet strengths. (18.75/75/200 mg, 25/100/200 mg, 31.25/125/200 mg, or 50/200/200 mg), Carbidopa + Levodopa + Entacapone tablet dosing should be carefully titrated for optimal clinical response. At the start of therapy, Carbidopa + Levodopa + Entacapone tablet should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.*

c) *When initiating Carbidopa + Levodopa + Entacapone tablet in patients currently treated with entacapone and levodopa/benserazide in a standard-release formulation, treatment should be stopped for one night and Carbidopa + Levodopa + Entacapone tablet therapy started the next morning. The therapy should begin with a dosage of Carbidopa + Levodopa + Entacapone tablet that will provide either the same amount of levodopa or slightly (5-10%) more*

Switching in patients not currently treated with entacapone to Carbidopa + Levodopa + Entacapone tablet

As with levodopa/ carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet. Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with

selectivity for MAO type B (e.g., selegiline HCl).

Initiation of Carbidopa + Levodopa + Entacapone tablet at a dosage corresponding to current treatment may be considered in some patients with Parkinson's disease and end-of-dose motor fluctuations who are not stabilised on their current standard-release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Carbidopa + Levodopa + Entacapone tablet is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Carbidopa + Levodopa + Entacapone tablet.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dosage by 10-30% within the first days to first weeks after initiating Carbidopa + Levodopa + Entacapone tablet treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

Dosage adjustment during the course of the treatment

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Carbidopa + Levodopa + Entacapone tablet should be considered, within the dosage recommendations.

When less levodopa is required, the total daily dosage of Carbidopa + Levodopa + Entacapone tablet should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Carbidopa + Levodopa + Entacapone tablet at an administration.

If other levodopa products are used concomitantly with a Carbidopa + Levodopa + Entacapone tablet, the maximum dosage recommendations should be followed.

Discontinuation of Carbidopa + Levodopa + Entacapone tablet therapy

If Carbidopa + Levodopa + Entacapone tablet treatment is discontinued and the patient is switched to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see section Special warnings and precautions for use, rhabdomyolisis).

Children and adolescents
The safety and efficacy of Carbidopa + Levodopa +

Entacapone tablet in patients under 18 years of age has not been established. Therefore the use of the medicinal product in patients under the age of 18 cannot be recommended.

Elderly
No adjustment of Carbidopa + Levodopa + Entacapone tablet dosage is necessary in elderly patients.

Hepatic impairment
Caution is recommended when administering Carbidopa + Levodopa + Entacapone tablet to patients with mild to moderate hepatic impairment. Dose reduction may be necessary (see section Pharmacokinetic properties).

Renal insufficiency
Renal insufficiency does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, and Carbidopa + Levodopa + Entacapone tablet should therefore be administered with caution in patients with severe renal impairment including those receiving dialysis therapies (see section Pharmacokinetic properties).

Method of administration
Each tablet is to be taken orally either with or without food (see section Pharmacokinetic properties). One tablet contains one treatment dose. The tablet should always be swallowed whole.

PENGANTAR

Obat dengan kombinasi zat aktif Carbidopa + Levodopa + Entecapone telah terdaftar di Indonesia. Carlepone dengan kombinasi Carbidopa 50 mg + Levodopa 200 mg + Entecapone 200 mg merupakan kekuatan baru yang merupakan kekuatan tertinggi dari kombinasi Carbidopa + Levodopa + Entecapone yang didaftarkan di Indonesia. Mengingat Carlepone merupakan penambahan kekuatan baru, saat ini evaluasi difokuskan pada data uji bioekivalensi untuk pembuktian efikasi dan keamanan lebih lanjut.

ASPEK MUTU

Carlepone kombinasi 50/200/200 tersedia dalam bentuk tablet salut selaput, mengandung Carbidopa 50 mg (54 mg as carbidopa monohydrate), Levodopa 200 mg, Entecapone 200 mg. Obat ini mengandung eksipien yang terdiri atas microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, povidone, isopropanol, magnesium stearate, purified water, maltodextrin, dan crospovidone, kombinasi-instacoat universal brown (A05G12308).

Zat Aktif

Carbidopa

Zat aktif carbidopa merupakan serbuk putih atau putih kekuningan dan telah dilakukan karakterisasi, diantaranya deskripsi, kelarutan, *specific optical rotation, chirality and isomers*.

Struktur kimia carbidopa telah ditunjukkan berdasarkan uji *elemental analysis, infrared spectra, uV spectra, NMR spectra, mass spectrum, x-ray diffraction, DSC and TG.* Komposisi elemen molekul carbidopa sesuai dengan carbidopa USP RS.

Spesifikasi carbidopa telah ditetapkan terdiri dari a*ppearance (visual), solubility, identification (specific rotation, UV, IR, color reaction with ferric chloride and cupri-tartaric), appearance solution, specific optical rotation, hydrazine, LOD, sulphated ash, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], particle size, residual solvent enantiomer [HPLC]), water content, residue on ignition,* dan *assay (potentiometry)*.

Uji stabilitas carbidopa telah dilakukan dan menunjukkan carbidopa stabil pada penyimpanan suhu 25°C. Hasil studi juga menunjukkan carbidopa tidak stabil ketika terpapar keadaan alkali, asam dan oksidasi.

Levodopa

Zat aktif levodopa merupakan serbuk kristal putih dan telah dikarakterisasi diantaranya deskripsi, kelarutan, *melting point, chirality, polymorphism*.

Struktur kimia levodopa telah ditunjukkan berdasarkan *MS, UV, IR, NMR (1 H-, 13C-NMR), X-ray diffractometer.*

Spesifikasi levodopa telah ditetapkan terdiri dari *appearance (visual), identification (IR), appearance solution, solubility, pH, LOD, Sulphate ash, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC]), residual solvent, particle size distribution* dan *assay (potentiometry)*.

Uji stabilitas levodopa telah dilakukan dan menunjukkan levodopa stabil ketika disimpan pada suhu 25°C. Hasil *stress degradation study* menunjukkan levodopa relatif stabil ketika terpapar suhu tinggi dan UV, tidak stabil pada keadaan basa.

Entacapone

Zat aktif entacapone merupakan serbuk kuning atau kuning kehijauan dan telah dikarakterisasi diantaranya deskripsi, kelarutan, pH, pKa, log P, *polymorphism*, *hygroscopicity, melting range, isomerism.*

Struktur kimia entecapone telah ditunjukkan berdasarkan uji *elementary analysis, MS, UV, IR, NMR (1 H-, 13C-NMR), mass spectrum, X-ray diffractogram, DSC, PXRD, TGA*. Entacapone yang dihasilkan terkonfirmasi dengan struktur entacapone form-A.

Spesifikasi entecapone telah ditetapkan terdiri dari *description (visual), solubility, identification (IR, XRD), purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC], residual solevt [GC]), LOD, particle size, polymorphism,* dan *assay (HPLC)*.

Uji stabilitas entecapone telah dilakukan dan menunjukkan entecapone stabil ketika disimpan pada suhu 25°C dan 30°C . Hasil *forced degradation study* menunjukkan entacapone tidak stabil ketika terpapar keadaan asam, basa dan oksidasi. Hasil uji *photostability* menunjukkan entacapone stabil terhadap pemanasan dan UV.

Obat jadi

Obat jadi diproduksi dalam bentuk sediaan tablet salut selaput berbentuk oval biconvex berwarna coklat.

Proses produksi dilakukan dengan proses granulasi basah, dan juga dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process controls*. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu *description (visual), identification (TLC, HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), LOD, residual solvents, microbial enumeration test and test for specified microorganisms* dan *assay (HPLC).* Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji bioekivalensi, data stabilitas jangka panjang, metode analisis dan data pengembangan proses yang relevant. Metode analisa yang digunakan telah divalidasi. Hasil

analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 24 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Kesimpulan
Dari aspek mutu, Obat Carlepone tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
Tidak ada studi non klinik yang diserahkan.

Studi Klinik
Telah diserahkan 2 studi bioekivalensi yaitu studi BEQ-1671-CLE(F)-2015 dan BEQ-2237-CLE(F)-2017 beserta uji disolusi terbanding antar kekuatan.

EVALUASI
Tidak dilakukan evaluasi terhadap studi non klinik mengingat zat aktif pada carlepone telah disetujui beredar di Indonesia sehingga evaluasi difokuskan pada studi bioekivalensi.

Studi Klinik
Evaluasi dilakukan pada 2 studi bioekivalensi yaitu studi BEQ-1671-CLE(F)-2015 dan BEQ-2237-CLE(F)-2017.

1. Hasil studi menunjukkan Carlepone Tablet Salut Selaput (Carbidopa/Levodopa/Entacapone 50/200/200 mg) bioekivalen terhadap obat pembanding Stalevo Tablet (Carbidopa/Levodopa/Entacapone 50/200/200 mg) berdasarkan hasil:
   - Nilai ratio GMR Cmax Carbidopa sebesar 101.44 (90%CI: 96 % – 107,18 %) dan nilai ratio GMR AUC0-T sebesar 101.38 (90%CI: 95,99% - 107,08%)
   - Nilai ratio GMR Cmax Levodopa sebesar 100,34 (90%CI: 96,67 % – 104,15 %) dan nilai ratio GMR AUC0-T sebesar 99,58 (90%CI: 97,48% - 101,74%).
   - Nilai ratio GMR Cmax Entecapone sebesar 89,93 (90%CI: 82,97 % – 97,48 %) dan nilai ratio GMR AUC0-T sebesar 98,05 (90%CI: 95,29% - 100,89%).
2. Hasil studi menunjukkan Carlepone Tablet Salut Selaput (Carbidopa/Levodopa/Entacapone 12,5/50/200 mg) bioekivalen terhadap obat pembanding Stalevo 50 (Carbidopa/Levodopa/Entacapone 12,5/50/200 mg) berdasarkan hasil:
   - Nilai ratio GMR Cmax Carbidopa sebesar 99,33 (90%CI: 92,48 % – 106,69 %) dan nilai ratio GMR AUC0-T sebesar 101,37 (90%CI: 94,24 % - 109,03)
   - Nilai ratio GMR Cmax Levodopa sebesar 100,67 (90%CI: 95,42 % – 106,20 %) dan nilai ratio GMR AUC0-T sebesar 95,97 (90%CI: 92,71 % - 99,35 %)
   - Nilai ratio GMR Cmax Entecapone sebesar 88,91 (90%CI: 80,12 % – 98,67 %) dan nilai ratio GMR AUC0-T sebesar 97,62 (90%CI: 93,96 % - 101,43 9%).
3. Formula Carlepone 4 kekuatan Carbidopa/Levodopa/Entacapone 50/200/200 mg, 31,25/125/200 mg, 25/100/200 mg, 18,75/75/200 mg yang didaftarkan menunjukkan proporsionalitas. Carlepone Tablet dengan formula bilayer yaitu layer formula Entecapone 200 mg yang sama dan konstan pada semua kekuatan, dan layer formula Carbidopa/Levodopa meningkat secara proporsional sesuai peningkatan kekuatan Carbidopa/Levodopa.
4. Hasil uji disolusi terbanding nilai F2 memenuhi syarat pada 4 medium (0,1N Hydrochloric acid; Phosphate buffer pH 5,5; Acetate buffer pH 4,5 dan Phosphate buffer pH 6,8) untuk Carlepone

31,25/125/200 mg, 25/100/200 mg, 18,75/75/200 mg terhadap Carlepone kekuatan terbesar 50/200/200 mg yang dilakukan studi bioekivalensi.

5. Adanya hubungan kausalitas penurunan hemoglobin berkaitan dengan obat, maka AE penurunan hemoglobin ditambahkan pada Brosur dan PIL.

KEPUTUSAN
Berdasarkan hal – hal tersebut diatas, Badan POM memutuskan bahwa registrasi kekuatan baru Carlepone 50/200/200 mg Tablet Salut Selaput diterima sesuai indikasi dan posologi yang diajukan.

Indication
Carbidopa + Levodopa + Entacapone tablet is indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment

Dosage and Administration
The optimum daily dosage must be determined by careful titration of levodopa in each patient. The daily dose should preferably be optimised using one of the four available tablet strengths (18.75/75/200mg, 25/100/200mg, 31.25/125/200mg or 50/200/200mg carbidopa/levodopa/entacapone).

Patients should be instructed to take only one Carbidopa + Levodopa + Entacapone tablet per dose administration. Patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting.
While the experience with total daily dosage greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2000 mg and therefore the maximum Carbidopa + Levodopa + Entacapone dose, for the Carbidopa + Levodopa + Entacapone strengths of 18.75/75/200mg, 25/100/200mg, 31.25/125/200mg is 10 tablets per day. Ten (10) tablets of Carbidopa + Levodopa + Entacapone tablet 150/37.5/200 mg equal 375 mg of carbidopa a day. Therefore, using maximum recommended daily dose of 375 mg of carbidopa, the maximum daily dose of Carbidopa + Levodopa + Entacapone tablet 50/200/200 mg is 7 tablets per day.
The maximum total daily levodopa dose administered in the form of Carbidopa + Levodopa + Entacapone tablet should not exceed 1500 mg.

Starting Carbidopa + Levodopa + Entacapone tablet therapy Switching from levodopa/ DDC inhibitor (carbidopa or benserazide) preparations and entacapone to Carbidopa + Levodopa + Entacapone tablet

Usually Carbidopa + Levodopa + Entacapone tablet is intended for use in patients already receiving treatment with corresponding doses of standard-release levodopa/DDC inhibitor and entacapone.
As with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet.
Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

a) *Patients who are currently receiving treatment with entacapone and standard-release levodopa/carbidopa in doses equal to Carbidopa + Levodopa + Entacapone tablet strengths can be directly switched to the corresponding Carbidopa + Levodopa + Entacapone tablet. For example:*

Levodopa/ Carbidopa	Entacapone	Equivalent Carbidopa + Levodopa + Entacapone tablet
100/25 mg	200 mg	25/100/200 mg

b) *When initiating Carbidopa + Levodopa + Entacapone tablet therapy in patients currently receiving treatment with entacapone and levodopa/carbidopa in doses not equal to the available Carbidopa + Levodopa + Entacapone tablet strengths. (18.75/75/200mg, 25/100/200mg, 31.25/125/200mg, or 50/200/200mg), Carbidopa + Levodopa + Entacapone tablet dosing should be carefully titrated for optimal clinical response. At the start of therapy, Carbidopa + Levodopa + Entacapone tablet should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.*
c) *When initiating Carbidopa + Levodopa + Entacapone tablet in patients currently treated with entacapone and levodopa/benserazide in a standard-release formulation, treatment should be stopped for one night and Carbidopa + Levodopa + Entacapone tablet therapy started the next morning. The therapy should begin with a dosage of Carbidopa + Levodopa + Entacapone tablet that will provide either the same amount of levodopa or slightly (5-10%) more.*

Switching in patients not currently treated with entacapone to Carbidopa + Levodopa + Entacapone tablet
As with levodopa/ carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet.Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

Initiation of Carbidopa + Levodopa + Entacapone tablet at a dosage corresponding to current treatment may be considered in some patients with Parkinson's disease and end-of-dose motor fluctuations who are not stabilised on their current standard-release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Carbidopa + Levodopa + Entacapone tablet is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Carbidopa + Levodopa + Entacapone tablet.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dosage by 10-30% within the first days to first weeks after initiating Carbidopa + Levodopa + Entacapone tablet treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

Dosage adjustment during the course of the treatment
When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Carbidopa + Levodopa + Entacapone tablet should be considered, within the dosage recommendations.

When less levodopa is required, the total daily dosage of Carbidopa + Levodopa + Entacapone tablet should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Carbidopa + Levodopa + Entacapone tablet at an administration.

If other levodopa products are used concomitantly with a Carbidopa + Levodopa + Entacapone tablet, the maximum dosage recommendations should be followed.

Discontinuation of Carbidopa + Levodopa + Entacapone tablet therapy
If Carbidopa + Levodopa + Entacapone tablet treatment is discontinued and the patient is switched to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see section Special warnings and precautions for use, rhabdomyolisis).

Children and adolescents
The safety and efficacy of Carbidopa + Levodopa + Entacapone tablet in patients under 18 years of age has not been established. Therefore the use of the medicinal product in patients under the age of 18 cannot be recommended.

Elderly
No adjustment of Carbidopa + Levodopa + Entacapone tablet dosage is necessary in elderly patients.

Hepatic impairment
Caution is recommended when administering Carbidopa + Levodopa + Entacapone tablet to patients with mild to moderate hepatic impairment. Dose reduction may be necessary (see section Pharmacokinetic properties).

Renal insufficiency
Renal insufficiency does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, and Carbidopa + Levodopa + Entacapone tablet should therefore be administered with caution in patients with severe renal impairment including those receiving dialysis therapies (see section Pharmacokinetic properties).

Method of administration
Each tablet is to be taken orally either with or without food (see section Pharmacokinetic properties). One tablet contains one treatment dose. The tablet should always be swallowed whole.

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benserazide) preparations and entacapone to Carbidopa + Levodopa + Entacapone tablet.

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100/25 mg	*200 mg*	*25/100/200 mg*

b) *When initiating Carbidopa + Levodopa + Entacapone tablet therapy in patients currently receiving treatment with entacapone and levodopa/carbidopa in doses not equal to the available Carbidopa + Levodopa + Entacapone tablet strengths. (18.75/75/200 mg, 25/100/200 mg, 31.25/125/200 mg, or 50/200/200 mg), Carbidopa + Levodopa + Entacapone tablet dosing should be carefully titrated for optimal clinical response. At the start of therapy, Carbidopa + Levodopa + Entacapone tablet should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.*

c) *When initiating Carbidopa + Levodopa + Entacapone tablet in patients currently treated with entacapone and levodopa/benserazide in a standard-release formulation, treatment should be stopped for one night and Carbidopa + Levodopa + Entacapone tablet therapy started the next morning. The therapy should begin with a dosage of Carbidopa + Levodopa +*

Entacapone tablet that will provide either the same amount of levodopa or slightly (5-10%) more

Switching in patients not currently treated with entacapone to Carbidopa + Levodopa + Entacapone tablet

As with levodopa/ carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet. Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

Initiation of Carbidopa + Levodopa + Entacapone tablet at a dosage corresponding to current treatment may be considered in some patients with Parkinson's disease and end-of-dose motor fluctuations who are not stabilised on their current standard-release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Carbidopa + Levodopa + Entacapone tablet is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Carbidopa + Levodopa + Entacapone tablet.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dosage by 10-30% within the first days to first weeks after initiating Carbidopa + Levodopa + Entacapone tablet treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

Dosage adjustment during the course of the treatment

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Carbidopa + Levodopa + Entacapone tablet should be considered, within the dosage recommendations.

When less levodopa is required, the total daily dosage of Carbidopa + Levodopa + Entacapone tablet should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Carbidopa + Levodopa +

Entacapone tablet at an administration.

If other levodopa products are used concomitantly with a Carbidopa + Levodopa + Entacapone tablet, the maximum dosage recommendations should be followed.

Discontinuation of Carbidopa + Levodopa + Entacapone tablet therapy

If Carbidopa + Levodopa + Entacapone tablet treatment is discontinued and the patient is switched to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see section Special warnings and precautions for use, rhabdomyolisis).

Children and adolescents
The safety and efficacy of Carbidopa + Levodopa + Entacapone tablet in patients under 18 years of age has not been established. Therefore the use of the medicinal product in patients under the age of 18 cannot be recommended.

Elderly
No adjustment of Carbidopa + Levodopa + Entacapone tablet dosage is necessary in elderly patients.

Hepatic impairment
Caution is recommended when administering Carbidopa + Levodopa + Entacapone tablet to patients with mild to moderate hepatic impairment. Dose reduction may be necessary (see section Pharmacokinetic properties).

Renal insufficiency
Renal insufficiency does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, and Carbidopa + Levodopa + Entacapone tablet should therefore be administered with caution in patients with severe renal impairment including those receiving dialysis therapies (see section Pharmacokinetic properties).

Method of administration
Each tablet is to be taken orally either with or without food (see section Pharmacokinetic properties). One tablet contains one treatment dose. The tablet should always be swallowed whole.

PENGANTAR

Obat dengan kombinasi zat aktif Carbidopa + Levodopa + Entecapone telah terdaftar di Indonesia. Carlepone dengan kombinasi Carbidopa 50 mg + Levodopa 200 mg + Entecapone 200 mg merupakan kekuatan baru yang merupakan kekuatan tertinggi dari kombinasi Carbidopa + Levodopa + Entecapone yang didaftarkan di Indonesia. Mengingat Carlepone merupakan penambahan kekuatan baru, saat ini evaluasi difokuskan pada data uji bioekivalensi untuk pembuktian efikasi dan keamanan lebih lanjut.

Drug product with the combination of active substances Carbidopa + Levodopa + Entacapone has been registered in Indonesia. Carlepone with the combination of Carbidopa 50 mg + Levodopa 200 mg + Entacapone 200 mg is a new strength which is the highest strength of the combination of Carbidopa + Levodopa + Entacapone registered in Indonesia. Given that Carlepone is a new strength addition, the evaluation is currently focused on bioequivalence test data for further proof of efficacy and safety.

ASPEK MUTU

Carlepone kombinasi 50/200/200 tersedia dalam bentuk tablet salut selaput, mengandung Carbidopa 50 mg (54 mg as carbidopa monohydrate), Levodopa 200 mg, Entecapone 200 mg. Obat ini mengandung eksipien yang terdiri atas microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, povidone, isopropanol, magnesium stearate, purified water, maltodextrin, dan crospovidone, kombinasi-instacoat universal brown (A05G12308).

Carlepone combination 50/200/200 is available in the form of film-coated tablets, containing Carbidopa 50 mg (54 mg as carbidopa monohydrate), Levodopa 200 mg, Entacapone 200 mg. This drug contains excipients consisting of microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, povidone, isopropanol, magnesium stearate, purified water, maltodextrin, crospovidone, and instacoat universal brown (A05G12308) combination.

Zat Aktif *Active Substance*

Carbidopa

Zat aktif carbidopa merupakan serbuk putih atau putih kekuningan dan telah dilakukan karakterisasi, diantaranya deskripsi, kelarutan, *specific optical rotation*, *chirality and isomers*.

The active substance of carbidopa is a white or yellowish-white powder and has been characterized, including description, solubility, specific optical rotation, chirality and isomers.

Struktur kimia carbidopa telah ditunjukkan berdasarkan uji *elemental analysis*, *infrared spectra*, *uV spectra*, *NMR spectra*, *mass spectrum*, *x-ray diffraction*, *DSC and TG*. Komposisi elemen molekul carbidopa sesuai dengan carbidopa USP RS.

The chemical structure of carbidopa has been shown based on elemental analysis, infrared spectra, UV spectra, NMR spectra, mass spectrum, x-ray diffraction, DSC and TG tests. The composition of the carbidopa's molecular elements corresponds to carbidopa USP RS.

Spesifikasi carbidopa telah ditetapkan terdiri dari a*ppearance (visual)*, *solubility*, *identification (specific rotation*, *UV*, *IR*, *color reaction with ferric chloride and cupri-tartaric)*, *appearance solution*, *specific optical rotation*, *hydrazine*, *LOD*, *sulphated ash*, *purity (heavy metals*, *related substances [high performance liquid chromatography (HPLC)]*, *particle size*, *residual solvent enantiomer [HPLC])*, *water content*, *residue on ignition*, dan *assay (potentiometry)*.

The specification of carbidopa has been set including appearance (visual), solubility, identification (specific rotation, UV, IR, color reaction with ferric chloride and cupri-tartaric), appearance solution, specific optical rotation, hydrazine, LOD, sulphated ash, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], particle size, residual solvent enantiomer [HPLC]), water content, residue on ignition, dan assay (potentiometry).

Uji stabilitas carbidopa telah dilakukan dan menunjukkan carbidopa stabil pada penyimpanan suhu 25°C. Hasil studi juga menunjukkan carbidopa tidak stabil ketika terpapar keadaan alkali, asam dan oksidasi.

Carbidopa stability tests have been carried out and show that carbidopa is stable at 25°C storage. The results of the study also showed that carbidopa was unstable when exposed to alkaline, acidic and oxidizing states.

Levodopa

Zat aktif levodopa merupakan serbuk kristal putih dan telah dikarakterisasi diantaranya deskripsi, kelarutan, *melting point*, *chirality*, *polymorphism*.

The active substance levodopa is a white crystalline powder and has been characterized by description, solubility, melting point, chirality, polymorphism.

Struktur kimia levodopa telah ditunjukkan berdasarkan *MS*, *UV*, *IR*, *NMR (1 H-*, *13C-NMR)*, *X-ray diffractometer*.

The chemical structure of levodopa has been shown based on MS, UV, IR, NMR (1 H-, 13C-NMR), X-RAY diffractometer.

Spesifikasi levodopa telah ditetapkan terdiri dari *appearance (visual)*, *identification (IR)*, *appearance solution*, *solubility*, *pH*, *LOD*, *Sulphate ash*, *purity (heavy metals*, *related substances [high performance liquid chromatography (HPLC)]*, *enantiomer [HPLC])*, *residual solvent*, *particle size distribution* dan *assay (potentiometry)*.

The specification of levodopa has been set including appearance (visual), identification (IR), appearance solution, solubility, pH, LOD, Sulphate ash, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC]), residual solvent, particle size distribution dan

assay (potentiometry).

Uji stabilitas levodopa telah dilakukan dan menunjukkan levodopa stabil ketika disimpan pada suhu 25°C. Hasil *stress degradation study* menunjukkan levodopa relatif stabil ketika terpapar suhu tinggi dan UV, tidak stabil pada keadaan basa.

Levodopa stability tests have been carried out and show that levodopa is stable when stored at 25°C. The results of the stress degradation study showed that levodopa was relatively stable when exposed to high temperatures and UV, unstable in an alkaline state.

Entacapone

Zat aktif entacapone merupakan serbuk kuning atau kuning kehijauan dan telah dikarakterisasi diantaranya deskripsi, kelarutan, pH, pKa, log P, *polymorphism*, *hygroscopicity*, *melting range*, *isomerism.*

The active substance entacapone is a yellow or greenish-yellow powder and has been characterized including description, solubility, pH, pKa, log P, polymorphism, hygroscopicity, melting range, isomerism.

Struktur kimia entacapone telah ditunjukkan berdasarkan uji *elementary analysis*, *MS*, *UV*, *IR*, *NMR (1 H-, 13C-NMR)*, *mass spectrum*, *X-ray diffractogram*, *DSC*, *PXRD*, *TGA*. Entacapone yang dihasilkan terkonfirmasi dengan struktur entacapone form-A.

The chemical structure of entacapone has been shown based on elementary analysis tests, MS, UV, IR, NMR (1 H-, 13C-NMR), mass spectrum, X-ray diffractogram, DSC, PXRD, TGA. The entacapone produced is confirmed with the structure of entacapone form-A.

Spesifikasi entecapone telah ditetapkan terdiri dari *description (visual)*, *solubility*, *identification (IR, XRD)*, *purity (heavy metals*, *related substances [high performance liquid chromatography (HPLC)]*, *enantiomer [HPLC]*, *residual solevt [GC])*, *LOD*, *particle size*, *polymorphism*, dan *assay (HPLC)*.

The specification of entacapone has been set including description (visual), solubility, identification (IR, XRD), purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC], residual solevt [GC]), LOD, particle size, polymorphism, dan assay (HPLC).

Uji stabilitas entecapone telah dilakukan dan menunjukkan entecapone stabil ketika disimpan pada suhu 25°C dan 30°C . Hasil *forced degradation study* menunjukkan entacapone tidak stabil ketika terpapar keadaan asam, basa dan oksidasi. Hasil uji *photostability* menunjukkan entacapone stabil terhadap pemanasan dan UV.

Entacapone stability tests have been conducted and show that entacapone is stable when stored at 25°C and 30°C. The results of forced degradation study showed that entacapone was unstable when exposed to acidic, alkaline and oxidation conditions. The results of the photostability test showed that entacapone was stable against heating and UV.

Obat jadi *Finished Product*

Obat jadi diproduksi dalam bentuk sediaan tablet salut selaput berbentuk oval biconvex berwarna coklat.

The finished product is produced in the form of brown oval-shaped film-coated tablet dosage.

Proses produksi dilakukan dengan proses granulasi basah, dan juga dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process controls*. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

The manufacturing process is carried out by wet granulation process, and critical stages are also identified, including in-process controls. Process validation has been carried out on 3 batches of commercial scale. The results of the validation process show the ability of the process to produce finished drugs that meet the set acceptance criteria.

Spesifikasi obat telah ditetapkan yaitu *description (visual), identification (TLC, HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), LOD, residual solvents, microbial enumeration test and test for specified microorganisms* dan *assay (HPLC).* Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji bioekivalensi, data stabilitas jangka panjang, metode analisis dan data pengembangan proses yang relevant. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Drug product specifications have been determined, namely description (visual), identification (TLC, HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), LOD, residual solvents, microbial enumeration test and test for specified microorganisms and assay (HPLC). The parameters in the specification were selected by considering, among others, the results of the batch test used in the bioequivalence test, long-term stability data, analytical methods and relevant process development data. The analytical method used has been validated. The results of batch analysis provide results that meet the required specifications.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 24 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Stability data from 3 batches of commercial-scale drug products have been carried out in zone IVB, namely at a temperature of 30°C/75% RH for 24 months and a temperature of 40°C/75% RH for 6 months with results that meet the required specifications.

Kesimpulan

Dari aspek mutu, Obat Carlepone tablet salut selaput dapat dipertimbangkan untuk diterima.

Conclusion

From the quality aspect, Carlepone film-coated tablets can be considered for acceptance.

ASPEK KHASIAT DAN KEAMANAN *EFFICACY AND SAFETY ASPECTS*

Studi Non Klinik *Non Clinical Study*

Tidak ada studi non klinik yang diserahkan. *No non-clinical studies were submitted.*

Studi Klinik *Clinical Study*

Telah diserahkan 2 studi bioekivalensi yaitu studi BEQ-1671-CLE(F)-2015 dan BEQ-2237-CLE(F)-2017 beserta uji disolusi terbanding antar kekuatan.

2 bioequivalence studies have been submitted, namely the BEQ-1671-CLE(F)-2015 and BEQ-2237-CLE(F)-2017 studies along with the comparative dissolution test between strengths.

EVALUASI *EVALUATION*

Tidak dilakukan evaluasi terhadap studi non klinik mengingat zat aktif pada carlepone telah disetujui beredar di Indonesia sehingga evaluasi difokuskan pada studi bioekivalensi.

No evaluation was carried out on non-clinical studies considering that the active substance in carlepone has been approved for distribution in Indonesia, therefore the evaluation is focused on bioequivalence studies.

Studi Klinik *Clinical Study*

Evaluasi dilakukan pada 2 studi bioekivalensi yaitu studi BEQ-1671-CLE(F)-2015 dan BEQ-2237-CLE(F)-2017.

The evaluation was carried out on 2 bioequivalence studies, namely the BEQ-1671-CLE(F)-2015 and BEQ-2237-CLE(F)-2017 studies.

1. Hasil studi menunjukkan Carlepone Tablet Salut Selaput (Carbidopa/Levodopa/Entacapone 50/200/200 mg) bioekivalen terhadap obat pembanding Stalevo Tablet (Carbidopa/Levodopa/Entacapone 50/200/200 mg) berdasarkan hasil:

   The results of the study showed that Carlepone Film Coated Tablets (Carbidopa/Levodopa/Entacapone 50/200/200 mg) were bioequivalent to the comparator drug Stalevo Tablets (Carbidopa/Levodopa/Entacapone 50/200/200 mg) based on the results:

   - Nilai ratio GMR Cmax Carbidopa sebesar 101.44 (90%CI: 96 % – 107,18 %) dan nilai ratio GMR AUC0-T sebesar 101.38 (90%CI: 95,99% - 107,08%)

     Carbidopa GMR ratio value of Cmax was 101.44 (90%CI: 96% – 107.18%) and the GMR ratio value AUC0-T was 101.38 (90%CI: 95.99% - 107.08%)

   - Nilai ratio GMR Cmax Levodopa sebesar 100,34 (90%CI: 96,67 % – 104,15 %) dan nilai ratio GMR AUC0-T sebesar 99,58 (90%CI: 97,48% - 101,74%).

     Levodopa GMR ratio value of Cmax was 100.34 (90%CI: 96.67% – 104.15%) and the GMR ratio of AUC0-T value was 99.58 (90%CI: 97.48% - 101.74%).

   - Nilai ratio GMR Cmax Entecapone sebesar 89,93 (90%CI: 82,97 % – 97,48 %) dan nilai ratio GMR AUC0-T sebesar 98,05 (90%CI: 95,29% - 100,89%).

     Entacapone GMR ratio value of Cmax was 89.93 (90%CI: 82.97% – 97.48%) and the GMR ratio value AUC0-T was 98.05 (90%CI: 95.29% - 100.89%).

2. Hasil studi menunjukkan Carlepone Tablet Salut Selaput (Carbidopa/Levodopa/Entacapone 12,5/50/200 mg) bioekivalen terhadap obat pembanding Stalevo 50 (Carbidopa/Levodopa/Entacapone 12,5/50/200 mg) berdasarkan hasil:

The results of the study showed that Carlepone Film Coated Tablets (Carbidopa/Levodopa/Entacapone 12.5/50/200 mg) were bioequivalent to the comparator drug Stalevo 50 (Carbidopa/Levodopa/Entacapone 12.5/50/200 mg) based on the results:

- Nilai ratio GMR Cmax Carbidopa sebesar 99,33 (90%CI: 92,48 % – 106,69 %) dan nilai ratio GMR AUC0-T sebesar 101,37 (90%CI: 94,24 % - 109,03)

  Carbidopa GMR ratio value of Cmax was 99.33 (90%CI: 92.48 % – 106.69 %) and the GMR ratio value AUC0-T was 101.37 (90%CI: 94.24 % - 109.03)

- Nilai ratio GMR Cmax Levodopa sebesar 100,67 (90%CI: 95,42 % – 106,20 %) dan nilai ratio GMR AUC0-T sebesar 95,97 (90%CI: 92,71 % - 99,35 %)

  Levodopa GMR Cmax ratio value was 100.67 (90%CI: 95.42 % – 106.20 %) and the GMR AUC0-T ratio value was 95.97 (90%CI: 92.71 % - 99.35 %)

- Nilai ratio GMR Cmax Entecapone sebesar 88,91 (90%CI: 80,12 % – 98,67 %) dan nilai ratio GMR AUC0-T sebesar 97,62 (90%CI: 93,96 % - 101,43 9%).

  Entacapone GMR ratio value of Cmax was 88.91 (90%CI: 80.12 % – 98.67 %) and the GMR ratio value AUC0-T was 97.62 (90%CI: 93.96 % - 101.43 9%).

3. Formula Carlepone 4 kekuatan Carbidopa/Levodopa/Entacapone 50/200/200 mg, 31,25/125/200 mg, 25/100/200 mg, 18,75/75/200 mg yang didaftarkan menunjukkan proporsionalitas. Carlepone Tablet dengan formula bilayer yaitu layer formula Entecapone 200 mg yang sama dan konstan pada semua kekuatan, dan layer formula Carbidopa/Levodopa meningkat secara proporsional sesuai peningkatan kekuatan Carbidopa/Levodopa.

   The registered 4 Carlepone strength formula of Carbidopa/Levodopa/Entacapone 50/200/200 mg, 31.25/125/200 mg, 25/100/200 mg, 18.75/75/200 mg shows proportionality. Carlepone Tablet has bilayer formula, consists of the same and constant 200 mg Entacapone formula layer at all strengths, and the Carbidopa/Levodopa formula layer increases proportionally according to the increase in Carbidopa/Levodopa strength.

4. Hasil uji disolusi terbanding nilai F2 memenuhi syarat pada 4 medium (0,1N Hydrochloric acid; Phosphate buffer pH 5,5; Acetate buffer pH 4,5 dan Phosphate buffer pH 6,8) untuk Carlepone 31,25/125/200 mg, 25/100/200 mg, 18,75/75/200 mg terhadap Carlepone kekuatan terbesar 50/200/200 mg yang dilakukan studi bioekivalensi.

   The F2 values of the comparative dissolution test meet the requirement for 4 mediums (0.1N Hydrochloric acid; Phosphate buffer pH 5.5; Acetate buffer pH 4.5 and Phosphate buffer pH 6.8) for Carlepone 31.25/125/200 mg, 25/100/200 mg, 18.75/75/200 mg against Carlepone with the highest strength of 50/200/200 mg in which the bioequivalence studies are performed.

5. Adanya hubungan kausalitas penurunan hemoglobin berkaitan dengan obat, maka AE penurunan hemoglobin ditambahkan pada Brosur dan PIL.

There is a causal relationship between hemoglobin decrease related to drugs, therefore hemoglobin decrease AE are added to the brochure and PIL.

KEPUTUSAN
Berdasarkan hal – hal tersebut diatas, Badan POM memutuskan bahwa registrasi kekuatan baru Carlepone 50/200/200 mg Tablet Salut Selaput diterima sesuai indikasi dan posologi yang diajukan.

Indication
Carbidopa + Levodopa + Entacapone tablet is indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment

Dosage and Administration
The optimum daily dosage must be determined by careful titration of levodopa in each patient. The daily dose should preferably be optimised using one of the four available tablet strengths (18.75/75/200mg, 25/100/200mg, 31.25/125/200mg or 50/200/200mg carbidopa/levodopa/entacapone).

Patients should be instructed to take only one Carbidopa + Levodopa + Entacapone tablet per dose administration. Patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting.
While the experience with total daily dosage greater than 200 mg carbidopa is limited, the maximum recommended daily dose of entacapone is 2000 mg and therefore the maximum Carbidopa + Levodopa + Entacapone dose, for the Carbidopa + Levodopa + Entacapone strengths of 18.75/75/200mg, 25/100/200mg, 31.25/125/200mg is 10 tablets per day. Ten (10) tablets of Carbidopa + Levodopa + Entacapone tablet 150/37.5/200 mg equal 375 mg of carbidopa a day. Therefore, using maximum recommended daily dose of 375 mg of carbidopa, the maximum daily dose of Carbidopa + Levodopa + Entacapone tablet 50/200/200 mg is 7 tablets per day.
The maximum total daily levodopa dose administered in the form of Carbidopa + Levodopa + Entacapone tablet should not exceed 1500 mg.

Starting Carbidopa + Levodopa + Entacapone tablet therapy Switching from levodopa/ DDC inhibitor (carbidopa or benserazide) preparations and entacapone to Carbidopa + Levodopa + Entacapone tablet

Usually Carbidopa + Levodopa + Entacapone tablet is intended for use in patients already receiving treatment with corresponding doses of standard-release levodopa/DDC inhibitor and entacapone.
As with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet.
Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

a) *Patients who are currently receiving treatment with entacapone and standard-release levodopa/carbidopa in doses equal to Carbidopa + Levodopa + Entacapone tablet strengths can be directly switched to the corresponding Carbidopa + Levodopa + Entacapone tablet. For example:*

Levodopa/ Carbidopa	Entacapone	Equivalent Carbidopa + Levodopa + Entacapone tablet
100/25 mg	200 mg	25/100/200 mg

b) *When initiating Carbidopa + Levodopa + Entacapone tablet therapy in patients currently receiving treatment with entacapone and levodopa/carbidopa in doses not equal to the available Carbidopa + Levodopa + Entacapone tablet strengths. (18.75/75/200mg, 25/100/200mg, 31.25/125/200mg, or 50/200/200mg), Carbidopa + Levodopa + Entacapone tablet dosing should be carefully titrated for optimal clinical response. At the start of therapy, Carbidopa + Levodopa + Entacapone tablet should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.*
c) *When initiating Carbidopa + Levodopa + Entacapone tablet in patients currently treated with entacapone and levodopa/benserazide in a standard-release formulation, treatment should be stopped for one night and Carbidopa + Levodopa + Entacapone tablet therapy started the next morning. The therapy should begin with a dosage of Carbidopa + Levodopa + Entacapone tablet that will provide either the same amount of levodopa or slightly (5-10%) more.*

Switching in patients not currently treated with entacapone to Carbidopa + Levodopa + Entacapone tablet
As with levodopa/ carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa + Levodopa + Entacapone tablet. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Carbidopa + Levodopa + Entacapone tablet.Carbidopa + Levodopa + Entacapone tablet may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl).

Initiation of Carbidopa + Levodopa + Entacapone tablet at a dosage corresponding to current treatment may be considered in some patients with Parkinson's disease and end-of-dose motor fluctuations who are not stabilised on their current standard-release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to Carbidopa + Levodopa + Entacapone tablet is not recommended for patients who have dyskinesias or whose daily levodopa dose is above 800 mg. In such patients it is advisable to introduce entacapone treatment as a separate medication (entacapone tablets) and adjust the levodopa dose if necessary, before switching to Carbidopa + Levodopa + Entacapone tablet.

Entacapone enhances the effects of levodopa. It may therefore be necessary, particularly in patients with dyskinesia, to reduce levodopa dosage by 10-30% within the first days to first weeks after initiating Carbidopa + Levodopa + Entacapone tablet treatment. The daily dose of levodopa can be reduced by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient.

Dosage adjustment during the course of the treatment
When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Carbidopa + Levodopa + Entacapone tablet should be considered, within the dosage recommendations.

When less levodopa is required, the total daily dosage of Carbidopa + Levodopa + Entacapone tablet should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Carbidopa + Levodopa + Entacapone tablet at an administration.

If other levodopa products are used concomitantly with a Carbidopa + Levodopa + Entacapone tablet, the maximum dosage recommendations should be followed.

Discontinuation of Carbidopa + Levodopa + Entacapone tablet therapy
If Carbidopa + Levodopa + Entacapone tablet treatment is discontinued and the patient is switched to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see section Special warnings and precautions for use, rhabdomyolisis).

Children and adolescents
The safety and efficacy of Carbidopa + Levodopa + Entacapone tablet in patients under 18 years of age has not been established. Therefore the use of the medicinal product in patients under the age of 18 cannot be recommended.

Elderly
No adjustment of Carbidopa + Levodopa + Entacapone tablet dosage is necessary in elderly patients.

Hepatic impairment
Caution is recommended when administering Carbidopa + Levodopa + Entacapone tablet to patients with mild to moderate hepatic impairment. Dose reduction may be necessary (see section Pharmacokinetic properties).

Renal insufficiency
Renal insufficiency does not affect the pharmacokinetics of entacapone. No specific studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency, and Carbidopa + Levodopa + Entacapone tablet should therefore be administered with caution in patients with severe renal impairment including those receiving dialysis therapies (see section Pharmacokinetic properties).

Method of administration
Each tablet is to be taken orally either with or without food (see section Pharmacokinetic properties). One tablet contains one treatment dose. The tablet should always be swallowed whole.