PACKAGE INSERT

1. Brand or Product Name

ANTIPAR 100 mg/25 mg/200 mg Film Coated Tablet
ANTIPAR 150 mg/37.5 mg/200 mg Film Coated Tablet

2. Name and Strength of Active Substance(s)

ANTIPAR 100 mg/25 mg/200 mg Film Coated Tablet: Each film-coated tablet contains 100 mg levodopa, 25 mg carbidopa and 200 mg entacapone.
ANTIPAR 150 mg/37.5 mg/200 mg Film Coated Tablet: Each film-coated tablet contains 150 mg levodopa, 37.5 mg carbidopa and 200 mg entacapone.

3. Product Description

ANTIPAR 100 mg/25 mg/ 200 mg Film Coated Tablet is a brown colored**,** oval, biconvex, unnotched film-coated tablet.
ANTIPAR 150 mg/37.5 mg/ 200 mg Film Coated Tablet is a brown colored**,** oval, biconvex, unnotched film-coated tablet.

List of Excipients

Hypromellose 2910
Sucrose
Polysorbate 80
Mannitol (E421)
Croscarmellose sodium
Polyvinylpyrrolidone
Magnesium stearate
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171)
Maize starch
Glycerol (E422)

4. Pharmacodynamics/Pharmacokinetics

4.1. Pharmacodynamics properties

Pharmacotherapeutic groups: Anti-parkinson dopaminergic drug
ATC code: N04B A03

Current information indicates that the symptoms of Parkinson's disease are related to depletion of dopamine amount in the *corpus striatum*. Giving dopamine directly to the patients with Parkinson's disease is not effective because of this compound cannot cross the blood-brain barrier. However, levodopa, which is the precursor of dopamine, crosses the blood-brain barrier and relieves the symptoms of the disease. As levodopa is extensively

metabolized in the periphery, only a small portion of a given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors.

Carbidopa and benserazide (peripheral DDC inhibitors) provide increasing of levodopa amount reached the brain by reducing the peripheral metabolism of levodopa to dopamine. When decarboxylation of levodopa is reduced with the co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse reactions such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, COMT, becomes the major peripheral metabolic pathway catalyzing the conversion of levodopa to 3-O-methyldopa (3-OMD), a potentially harmful metabolite of levodopa. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased AUC in the pharmacokinetic profile of levodopa. Consequently, the clinical response to each dose of levodopa is enhanced and prolonged.

The evidence of the therapeutic effects of levodopa/carbidopa/entacapone is based on two phase III double-blind studies. In these studies, 376 Parkinson's disease patients with end-of-dose motor fluctuations received either entacapone or placebo with each levodopa/DDC inhibitor dose. Daily time without symptoms (ON) of cases with and without entacapone was recorded in home-diaries by patients. In the first study, entacapone increased the mean daily ON time by 1 h 20 min. (CI (Confidence Interval) 95% 45 min., 1 h 56 min.) from baseline. This corresponds to an 8.3% increase in the proportion of daily ON time. Correspondingly, the decrease in daily OFF time was 24% in the entacapone group and 0% in the placebo group. In the second study, the mean proportion of daily ON time increased by 4.5% (CI (Confidence Interval) 95% 0.93%, 7.97%) from baseline. This is translated to a mean increase of 35 min. in the daily ON time. Correspondingly, the daily OFF time decreased by 18% on entacapone and by 5% on placebo. Because the effects of ANTIPAR tablets are equivalent with entacapone 200 mg tablet administered concomitantly with standard release carbidopa/levodopa preparations in corresponding doses these results are applicable to describe the effects of ANTIPAR as well.

4.2. Pharmacokinetic properties

General characteristics

Absorption:

There is substantial inter- and intra-individual variability in the absorption of levodopa, carbidopa and entacapone. Levodopa and entacapone are rapidly absorbed and eliminated. Carbidopa is absorbed and eliminated slightly slower compared with levodopa. When given separately without the two other active substances, the bioavailability for levodopa is 15-33%, for carbidopa 40-70% and for entacapone 35% after a 200 mg oral dose. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. The absorption of entacapone is not significantly affected from food.

Distribution:
When the distribution volume of both levodopa (Vd 0.36-1.6 L/kg) and entacapone (Vd_{SS} 0.27 L/kg) is moderately small, no data for carbidopa are available.

Levodopa is bound to plasma protein only to a minor extent of about 10-30%. This ratio is approximately 36% for carbidopa. Entacapone is extensively bound to plasma proteins (about 98%), mainly to serum albumin. At therapeutic concentrations, entacapone does not displace other extensively bound active substances (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam) and cannot be significantly removed from the protein by any of them at therapeutic or higher concentrations.

Biotransformation:
Levodopa is extensively metabolized to various metabolite. *O*-methylation by COMT enzyme and decarboxylation by DDC are the most important pathways.

Carbidopa has two major metabolites, α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3, 4-dihydroxy-phenylpropionic acid. These are excreted primarily through the kidneys as unchanged or conjugated with glucuronic acid. 30% of the urinary excretion part of the administered dose is in the form of unchanged carbidopa.
Entacapone is almost completely metabolized prior to excretion via urine (10%-20%) and bile/faeces (80%-90%). The main metabolic pathway is glucuronidation of entacapone and its just one active metabolite, the cis-isomer (accounts for about 5% of plasma amount).

Elimination:
Total clearance for levodopa is in the range of 0.55-1.38 L/kg/h and for entacapone is in the range of 0.70 L/kg/h. The elimination-half life ($t_{½}$) is 0.6-1.3 hours for levodopa, 2-3 hours for carbidopa and 0.4-0.7 hours for entacapone.
Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs on repeated administration.
Data from in vitro studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 μM) enzyme. Entacapone inhibited no or little of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19) (See section 10. Interaction with other medicines and other forms of interaction).

Characteristics in patients
Renal impairment:
Renal impairment does not affect the pharmacokinetics of entacapone. No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. However, a longer dosing interval of ANTIPAR may be considered for patients who are receiving dialysis treatment.

Hepatic impairment:
The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both

in the absorption and elimination periods. No particular studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment are reported.

Geriatric population:
When given without carbidopa and entacapone, the absorption of levodopa is greater and elimination is slower in elderly than in young people. However, after combination of carbidopa with levodopa, the absorption of levodopa is similar between the elderly and the young people, but the AUC maintained its feature that 1.5 fold greater in the elderly due to lower clearance and decreased DDC activity by aging.
There are no significant differences in the AUC of carbidopa or entacapone between younger (45–64 years) and elderly (65–75 years).

Gender:
Bioavailability of levodopa is significantly higher in women than in men. In the pharmacokinetic studies with levodopa/carbidopa/entacapone, the bioavailability of levodopa is higher in women than in men, primarily due to the difference in body weight, while there is no gender difference with carbidopa and entacapone.

4.3. Preclinical safety data
Preclinical data of levodopa, carbidopa and entacapone, tested alone or in combination, suggested that there cannot be special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In repeated dose toxicity studies with entacapone, anemia most likely due to iron chelating properties of entacapone was observed. Regarding reproduction toxicity of entacapone, decreased fetal weight and a slightly delayed bone development were noticed in rabbits treated at systemic exposure levels in the therapeutic range. Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits.

5. Indications
ANTIPAR 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.

6. Recommended Dosage
Unless otherwise advised by doctor;

The optimum daily ANTIPAR dose should be determined by careful titration of levodopa for each patient. The daily ANTIPAR dose should be optimized using one of the preferred tablet strengths (100 mg/25 mg/200 mg or 150 mg/37.5 mg/200 mg levodopa/carbidopa/entacapone). If the required dose could not be achieved by the 100mg/25mg/200mg or 150mg/37.5mg/200mg strengths other levodopa/carbidopa/entacapone products should be used.

Patients should be instructed to take only one ANTIPAR tablet per dose administration. While the experience with total daily dose greater than 200 mg of carbidopa is limited, but in patients receiving less than 70-100 mg carbidopa a day, possibility of nausea and vomiting are

high. The maximum recommended daily dose of entacapone is 2000 mg and therefore the maximum ANTIPAR dose is 10 tablets per day for the ANTIPAR 100 mg/25 mg/200 mg, and 150 mg/37.5 mg/200 mg. Ten (10) tablets of ANTIPAR 150 mg/37.5 mg/200 mg equals 375 mg of carbidopa a day. The maximum recommended daily dose of carbidopa is 375 mg.

The maximum daily levodopa dose to be administered during ANTIPAR treatment should not exceed 1500 mg.

Start to ANTIPAR treatment:

How to transfer patients taking levodopa/dopa decarboxylase (DDC) inhibitor (carbidopa or benserazide) preparations and entacapone tablets to ANTIPAR administration:

ANTIPAR is generally for use in patients treated with the equivalent standard release doses of levodopa/DDC inhibitor and entacapone.

Like with levodopa/carbidopa, non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with ANTIPAR. These inhibitors must be discontinued at least two weeks before starting ANTIPAR treatment. ANTIPAR can be administered concurrently with the manufacturer's recommended doses of MAO inhibitors with selectivity for MAO type B (e.g. selegiline HCl).

a) Patients who are currently treated with entacapone and standard release levodopa/carbidopa equivalent to ANTIPAR tablet dose can be directly transferred to equivalent ANTIPAR tablet.

Levodopa/Carbidopa	**Entacapone**	**Equivalent ANTIPAR**
100 mg/25 mg	200 mg	100 mg/25 mg/200 mg
150 mg/37.5 mg	200 mg	150 mg/37.5 mg/200 mg

b) When initiating ANTIPAR treatment in patients currently treated with entacapone and levodopa/carbidopa in doses not equal to Antipar 100 mg/25 mg/200 mg or 150mg/37.5 mg/200 mg, ANTIPAR dosing should be carefully titrated for optimal clinical response. At the initiation, ANTIPAR should be adjusted to correspond as closely as possible to the total daily dose of levodopa currently used.

c) When initiating ANTIPAR treatment in patients currently treated with entacapone and levodopa/benserazide in a standard release formulation, the dosing of levodopa/benserazide should be discontinued in the previous night, and ANTIPAR administration is started in the next morning. The starting dose of ANTIPAR should provide either the same amount of levodopa or slightly more (5%-10%).

d) There are no data on transferring patients from controlled-release formulations or standard release preparations with a 10:1 ratio of levodopa/DDC inhibitor to ANTIPAR.

How to transfer patients not currently treated with entacapone to ANTIPAR administration

Like with levodopa/carbidopa, concomitant use of non-selective monoamine oxidase (MAO) inhibitors with ANTIPAR is contraindicated. These inhibitors must be discontinued at least two weeks before starting ANTIPAR treatment. ANTIPAR can be administered concurrently with the manufacturer's recommended doses of MAO inhibitors with selectivity for MAO type B (e.g. selegiline HCl).

Initiation of ANTIPAR may be considered at corresponding doses to current treatment in some patients with Parkinson disease and end-of-dose motor fluctuations, who are not stabilized on their current standard release levodopa/DDC inhibitor treatment. However, a direct switch from levodopa/DDC inhibitor to ANTIPAR is not recommended for patients who have dyskinesia or whose daily levodopa dose is above 600 mg. In such patients, entacapone treatment should be administered as a separate medication (entacapone tablet) and adjust the levodopa dose if necessary, before switching to ANTIPAR.

Entacapone enhances the effects of levodopa. Therefore, it may be necessary, particularly in patients with dyskinesia, to reduce levodopa dose by 10%-30% within the first days to first weeks after initiating ANTIPAR 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.

Dose 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 dosage of ANTIPAR should be considered, within the dose recommendations mentioned under Recommended Dosage section.

When less levodopa is required, the total daily dose of ANTIPAR should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of ANTIPAR at an administration.

If other levodopa products are used concomitantly with ANTIPAR tablet; the maximum dose recommendations should be followed.

Discontinuation of ANTIPAR treatment

If ANTIPAR (levodopa/carbidopa/entacapone) treatment is discontinued and the patient is transferred to levodopa/DDC inhibitor treatment without entacapone, it is necessary to adjust the dosing of other anti-parkinson treatments, especially levodopa, to achieve a sufficient level of control of the parkinson symptoms. (See section 9. Warnings and precautions, rhabdomyolysis)

Additional information on special populations:

Renal impairment:

No particular studies are reported on the pharmacokinetics of levodopa and carbidopa in patients with renal insufficiency. Therefore, ANTIPAR treatment should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapies

(See section 4.2 Pharmacokinetic properties). Renal impairment does not affect the pharmacokinetics of entacapone.

Pediatric population:
The safety and efficacy of ANTIPAR in children aged below 18 years (children and adolescents) have not been established. No other data are available. ANTIPAR is not recommended for use in children below age of 18.

Geriatric population
No dose adjustment of ANTIPAR is required for elder patients.

7. Mode/Route of Administration

ANTIPAR should be taken orally, with or without food (see section 4.2 Pharmacokinetic properties). One tablet contains one treatment dose and tablets should always be taken without splitting as a whole tablet.

8. Contraindications

- Hypersensitivity to the levodopa, carbidopa and entacapone or any excipients in formulation,
- Liver impairment,
- Narrow-angle glaucoma,
- Pheochromocytoma,
- Co-administration of ANTIPAR with non-selective monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine).
- Co-administration with a selective MAO-A inhibitor and a selective MAO-B inhibitor (See section 10. Interaction with other medicines and other forms of interaction, other anti-parkinson drugs.) These inhibitors should be discontinued at least two weeks before starting ANTIPAR treatment.
- A previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.
- Because levodopa may activate malignant melanoma, ANTIPAR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

9. Warning and Precautions

ANTIPAR is not recommended for the treatment of drug-induced extrapyramidal reactions.
ANTIPAR treatment should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease or history of peptic ulcer disease or history of convulsions.

In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dose adjustments.

All patients treated with ANTIPAR should be monitored carefully for the development of

mental changes (e.g. hallucinations and psychoses), depression with suicidal tendencies, and serious antisocial behaviors. Patients with past or current psychosis should be treated with caution.

Concomitant administration of antipsychotics with dopamine receptor-blocking properties, particularly D_2 receptor antagonists should be carried out with caution, and the patient carefully observed for loss of anti-parkinson effect or worsening of parkinson symptoms.

Should be careful during the ANTIPAR treatment of patients with chronic wide-angle glaucoma and the intra-ocular pressure control should be provided well and the patient should be monitored carefully for pressure changes.

ANTIPAR may induce orthostatic hypotension. Therefore, ANTIPAR should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.

Entacapone is associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease when co-administered with levodopa and therefore caution should be exercised when driving or operating machines (See section 12. Drive and use machines).

In clinical studies, dopaminergic adverse reactions, e.g. dyskinesia, were observed more common in patients who are administered entacapone and dopamine agonists (such as bromocriptine), selegiline or amantadine compared to those who received placebo with this combination. The doses of other anti-parkinson medicinal products may need to be adjusted when ANTIPAR treatment is introduced in a patient not previously treated with entacapone.

Rhabdomyolysis secondary to severe dyskinesias or Neuroleptic Malignant Syndrome (NMS) has been observed rarely in patients with Parkinson's disease. Isolated cases of rhabdomyolysis have been reported with entacapone treatment. In scope of this, NMS including rhabdomyolysis and hyperthermia is characterized by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g., agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase level. In each case, only some of these symptoms and/or findings may be evident. The early diagnosis is important for the appropriate management of NMS. A syndrome resembling the NMS including symptoms and findings like muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase level has been reported with the abrupt withdrawal of anti-parkinson drugs. Isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone.

When considered necessary, ANTIPAR treatment or other dopaminergic treatment should be interrupted slowly. If symptoms and/or findings are observed even ANTIPAR treatment is interrupted slowly, increase in levodopa dose may be necessary.

Doctors should be careful when deciding that switch from ANTIPAR to an entacapone-free levodopa/DDC inhibitor treatment for their patients. When considered necessary, ANTIPAR treatment or other dopaminergic treatment should be interrupted slowly and increase in levodopa dose may be necessary.

Dopamine dysregulation syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see section 13. Undesirable effects).

If general anaesthesia is required, treatment with ANTIPAR may be continued for as long as the patient is permitted to take fluids and drug by mouth. If treatment has to be stopped temporarily, ANTIPAR may be restarted as soon as oral drug can be taken at the same daily dose as before.

Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during long-term treatment with ANTIPAR.

For patients experiencing diarrhoea, a follow-up of weight is recommended in order to avoid potential excessive weight decrease. Prolonged or persistent diarrhea appearing during use of ANTIPAR, may be a sign of colitis. In the case of prolonged or persistent diarrhoea, the drug should be discontinued and appropriate medical treatment and investigations considered.

For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.

Patients should be regularly monitored for the development of impulse control disorders. Patients and their careers should be made aware that behavioral symptoms of impulse control disorders including pathological gambling, increased libido, hyper sexuality, 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 ANTIPAR. Review of treatment is recommended if such symptoms develop.

Levodopa/carbidopa may cause false positive result if a dipstick is used to test for urinary ketone and this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may cause false negative results for glycosuria.

ANTIPAR tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this drug.

ANTIPAR 100 mg/25 mg/200 mg Film Coated Tablet contains <8.07 mg sodium per tablet. This is equivalent to <4% of the recommended maximum daily dietary intake of sodium for an adult (for 10 tablets). To be taken into consideration for patients with controlled sodium diet.

ANTIPAR 150 mg/37.5 mg/200 mg Film Coated Tablet contains <9.1 mg sodium per tablet. This is equivalent to <4.55% of the recommended maximum daily dietary intake of sodium for an adult (for 10 tablets). To be taken into consideration for patients with controlled sodium diet.

10. Interaction with Other Medicines and Other Forms of Interaction

Interactions with other anti-parkinson drugs:

To date there has been no indication of interactions that would preclude concurrent use of standard anti-parkinson drugs with ANTIPAR treatment.

Entacapone given in high doses may affect the absorption of carbidopa. However, no interaction with carbidopa has been observed with the recommended treatment schedule (200 mg of entacapone up to 10 times daily). Interactions between entacapone and selegiline have been investigated in repeated dose studies in Parkinson's disease patients treated with levodopa/DDC inhibitor and no interaction was observed. When used with ANTIPAR, the daily dose of selegiline should not exceed 10 mg.

ANTIPAR should not used concurrently with Comtan (entacapone) due to ANTIPAR contains entacapone.

It should be taken consideration when below active ingredients are administered concomitantly with levodopa treatment.

Interactions with antihypertensive drugs:

Symptomatic postural hypotension may occur when levodopa is added to the treatment of patients already receiving antihypertensive drugs. Dose adjustment of the antihypertensive agents may be required.

Interactions with antidepressants:

Rarely, side effects including hypertension and dyskinesia have been reported with the concomitant use of levodopa/carbidopa and tricyclic antidepressants. Interactions between entacapone and imipramine and between entacapone and moclobemide have been investigated in single dose studies in healthy volunteers. No pharmacodynamic interactions have been observed. A significant number of patients with parkinson disease have been treated with the combination of levodopa, carbidopa and entacapone with several active substances including noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine, tricyclic antidepressants and MAO-A inhibitors with drugs (e.g. catechol-structured compounds, rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa, apomorphine and paroxetine) that are metabolised by COMT (catechol-O-methyl transferase). No pharmacodynamic interactions have been observed. However, caution should be exercised when these drugs are used concomitantly with ANTIPAR (see sections 8. Contraindications and 9. Warnings and precautions).

Interactions with other drugs:

Dopamine receptor antagonists (e.g. some antipsychotics and antiemetic), phenytoin and papaverine may reduce the therapeutic effect of levodopa. Patients taking these drugs with ANTIPAR should be carefully observed for loss of therapeutic response.

Due to entacapone's affinity to cytochrome P450 2C9 *in-vitro* (see section 4.2 Pharmacokinetic properties), ANTIPAR may potentially interfere with active substances whose metabolism is dependent on this isoenzyme, such as S-warfarin. However, in an interaction study with healthy volunteers, entacapone did not change the plasma levels of S-warfarin, while the AUC for R-warfarin increased on average by 18% [CI_{90} 11%-26%]. The INR values increased on average by 13% [CI_{90} 6%-19%]. Thus, a control of INR is

recommended when ANTIPAR is initiated for patients receiving warfarin.

Other forms of interactions:

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

Levodopa and entacapone may form chelates with iron in the gastrointestinal tract. Therefore, ANTIPAR and iron preparations should be taken at least 2-3 hours apart (see section 13. Undesirable effects).

ANTIPAR may be given to patients with Parkinson's disease who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

Because of its mechanism of action, entacapone may interfere with the metabolism of medicinal products containing a catechol group and potentiate their action. Thus, entacapone should be administered cautiously to patients being treated with medicinal products metabolized by catechol-O-methyl transferase (COMT), e.g. rimiterol, isoprenaline, adrenaline, noradrenalin, dopamine, dobutamine, alpha-methyldopa apomorphine.

In vitro data:

Entacapone binds to human albumin binding site II which also binds several other medicinal products, including diazepam and ibuprofen. According to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of the drugs. Accordingly, to date there has been no indication of such interactions.

11. Use during Pregnancy/Lactation

There are no adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicity of the separate compounds (see section 4.3 Preclinical safety data). The potential risk for humans is unknown. ANTIPAR should not be used in during pregnancy.

Lactation

Levodopa is excreted in human breast milk. There is evidence that lactation is suppressed during treatment with levodopa. It has been found that carbidopa and entacapone are excreted in breast milk in animal studies, but it is not known whether they are excreted in human breast milk. The safety of levodopa, carbidopa or entacapone in the infant is not known. Women should not breast-feed during treatment with ANTIPAR.

Reproductivity / Fertility

No adverse reaction on fertility has been observed in preclinical studies with entacapone, carbidopa or levodopa alone. Fertility studies in animals have not been conducted with the combination of entacapone, levodopa and carbidopa.

12. Drive and Use Machines

Levodopa/carbidopa/entacapone may have major effects on the ability to drive and use machines. Levodopa, carbidopa and entacapone together may cause dizziness and

symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines.

Patients treated with ANTIPAR and present somnolence and/or sudden sleep onset episodes must be instructed 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 have resolved (see section 9. Warnings and precautions).

13. Undesirable Effects

The most frequently reported adverse reactions with levodopa/carbidopa/entacapone are dyskinesias occurring in approximately 19% of patients; gastrointestinal symptoms including nausea and diarrhoea occurring in approximately 15% and 12% of patients, respectively; muscle, musculoskeletal and connective tissue pain occurring in approximately 12% of patients; and harmless reddish-brown discolouration of urine occurring in approximately 10% of patients. Serious events of gastrointestinal hemorrhage (uncommon) and angioedema (rare) have been identified from the clinical trials with levodopa/carbidopa/entacapone or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur although no cases have been identified from the clinical trial data.

The following adverse reactions have been accumulated from data of eleven double-blind clinical trials consisting of 3230 patients (1810 treated with levodopa/carbidopa/entacapone combined with levodopa/DDC inhibitor or entacapone, and 1420 treated with placebo combined with levodopa/DDC inhibitor or cabergoline combined with levodopa/DDC inhibitor), and from the post-marketing data since the introduction of entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare(<1/10,000), not known (cannot be estimated from the available data); isolated notifications include. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Blood and lymphatic system disorders
Common: Anaemia
Uncommon: Thrombocytopenia

Metabolism and nutrition disorders
Common: Weight decreased*, decreased appetite*

Psychiatric disorders
Common: Depression, hallucination, confusional state*, abnormal dreams*, anxiety, insomnia
Uncommon: Psychosis, agitation*
Not known: Suicidal behavior, delusions, euphoria, dopamine dysregulation syndrome

Nervous system disorders
Very common: Dyskinesia*

Common: Parkinsonism aggravated (e.g. bradykinesia)*, tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness*, headache
Rare: Paraesthesia
Not known: Neuroleptic malignant syndrome*, ataxia, numbness, bitter taste

Eye disorders
Common: Blurred vision
Not known: Diplopia

Cardiac disorders
Common: Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris) **, irregular heart rhythm
Uncommon: Myocardial infarction**

Vascular disorders
Common: Orthostatic hypotension, hypertension
Uncommon: Gastrointestinal hemorrhage
Rare: Phlebitis
Not known: Flushing, hot flush

Respiratory system disorders
Common: Dyspnoea
Not known: Hiccupps, dysphonia

Gastrointestinal disorders
Very common: Diarrhoea*, nausea*
Common: Constipation*, vomiting*, dyspepsia, abdominal pain and discomfort*, dry mouth*
Uncommon: Colitis*, dysphagia
Rare: Development of duodenal ulcer
Not known: Salivary hypersecretion, bruxism, flatulence, glossodynia

Hepato-biliary disorders
Uncommon: Abnormal hepatic function tests*
Not known: Hepatitis with mainly cholestatic features (See section 9)*

Skin and subcutaneous tissue disorders
Common: Rash*, hyperhidrosis
Uncommon: Discolourations other than urine (e.g. skin, nail, hair, sweat)*
Rare: Angioedema
Not known: Urticaria*, alopecia

Musculoskeletal and connective tissue disorders
Very common: Muscle, musculoskeletal and connective tissue pain*
Common: Muscle spasms, arthralgia
Not known: Rhabdomyolysis*

Renal and urinary disorders
Very common: Chromaturia*
Common: Urinary tract infection
Uncommon: Urinary retention

General disorders and administration site conditions
Common: Chest pain, peripheral oedema, fall, gait disturbance, asthenia, fatigue
Uncommon: Malaise

**Adverse reactions that are mainly attributable to entacapone or are more frequent (by the frequency difference of at least 1% in the clinical trial data) with entacapone than levodopa/DDC inhibitor alone.*

***The incidence rates of myocardial infarction and other ischemic heart disease events (0.43% and 1.54%, respectively) are obtained from an analysis of 13 double-blind studies involving 2082 patients with end-of-dose motor fluctuations receiving entacapone.*

Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk above. Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat. Other adverse reactions with an asterisk above are marked based on either their more frequent occurring (by the frequency difference of at least 1%) in the clinical trial data with entacapone than levodopa/DDC alone or the individual case safety reports received after the introduction of entacapone into the market.

Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa treatment has not been established.

Dopamine dysregulation syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/carbidopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see section 9. Warning and precautions).

Impulse control disorders: Pathological gambling, increased libido, hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including levodopa/carbidopa/entacapone (See section 9. Warnings and precautions)

Entacapone with levodopa has been associated with cases of excessive daytime somnolence and sudden sleep onset episodes.

Laboratory tests

The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and should, therefore, be borne in mind when treating patients with ANTIPAR: Transient abnormalities include elevated values of blood urea. Elevated serum glucose and blood in the urine have been reported.

14. Overdose and Treatment

The post-marketing data includes isolated cases of overdose in which the reported highest daily doses of levodopa and entacapone have been at least 10,000 mg and 40,000 mg, respectively. The acute symptoms and signs in these cases of overdose included agitation, confusional state, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration contained discolourations of skin, tongue and conjunctiva, and chromaturia. To do things of acute overdose with ANTIPAR is similar to acute overdose with levodopa. Hospitalization is advised and general supportive measures should be employed with immediate gastric lavage and repeated doses of charcoal over time. This may hasten the elimination of entacapone in particular by decreasing its absorption and reabsorption from the gastrointestinal system. The adequacy of the respiratory, circulatory and renal systems should be carefully monitored and appropriate supportive measures employed. ECG monitoring should be started and the patient carefully monitored for the possible development of arrhythmias. If required, appropriate anti-arrhythmic treatment should be administered. The possibility that the patient has taken other active substances in addition to ANTIPAR should be taken into consideration. The role of dialysis in the treatment of overdose is not known.

15. Incompatibilities

Not applicable.

16. Storage Condition

Store under room temperature 30°C.
Also, store at or below 30°C up to 100 days after first opening.

17. Shelf Life

24 months.

18. Dosage Form or Presentation

In HDPE bottle with a child resistant cap containing 100 tablets and in a cardboard box.

19. Name and Address of Manufacturer and Product Registrant

Manufacturer: İlko İlaç San. ve Tic. A.Ş.
3.Organize Sanayi Bölgesi, Kuddusi Cad., 23. Sok., No: 1
Selçuklu/ Konya, Turkey

Product Registrant: Goldplus Universal Pte. Ltd.
103 Kallang Avenue #06-02, Singapore 339504