SUMMARY OF PRODUCT CHARACTERISTICS

DOPICAR

Tablets

1 NAME OF THE MEDICINAL PRODUCT

Dopicar Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Dopicar contains
Levodopa 250 mg
Carbidopa 25 mg

For the full list of excipients see section 6.1 - "List of excipients".

3. PHARMACEUTICAL FORM

Tablets.

Blue slightly spotted white, round flat tablet with beveled edges, engraved 'TEVA' on one side and quadrisected on the other.

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms associated with Parkinson's disease.

4.2 Posology and method of administration

Posology
The optimum daily dosage of Dopicar must be determined by careful titration in each patient.

Dopicar Tablets are available in a ratio of 1:10 of carbidopa to levodopa

Most patients can be maintained on 3-6 tablets of Dopicar a day, given in divided doses.

The maximum dosage should not exceed 8 tablets of Dopicar a day, since experience with total daily dosages of carbidopa greater than 200 mg is limited. If further titration of dosage is desired, levodopa should be added to the treatment regimen.

General considerations
Studies show that the peripheral dopa-decarboxylase is fully inhibited (saturated) by carbidopa at doses between 70 and 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Patients who require only low doses of levodopa (e.g. less than 700 mg

when given as Dopicar), will receive doses of carbidopa which theoretically do not saturate peripheral dopa decarboxylase**.**

Standard antiparkinsonian drugs, other than levodopa alone, may be continued while Dopicar is being administered, although their dosage may have to be adjusted.

Because both therapeutic and adverse effects are seen more rapidly with Dopicar than with levodopa, patients should be carefully monitored during the dosage adjustment period. Involuntary movements, particularly blepharospasm, are a useful early sign of excess dosage in some patients.

Patients not currently receiving levodopa

Dosage may be best initiated with half tablet of Dopicar 3 times a day and increased by half a tablet every day or every other day, until a dosage of 3 tablets a day is reached.

If further titration is necessary, dosage with Dopicar may be increased by half or one tablet every day or every other day, to a maximum of 8 tablets a day. Alternatively, dosage may be titrated to 6 tablets of Dopicar a day, and further adjusted with increments of levodopa.

Because both therapeutic and adverse responses occurmore rapidly with Dopicar than when levodopa is administered, patients should be monitored closely during the dosage adjustment period. Specifically, involuntary movements will occur more rapidly with Dopicar than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Patients receiving levodopa

Levodopa must be discontinued at least 12 hours before Dopicar therapy is initiate. The easiest way to move patients from therapy with levodopa to Dopicar is to initiate Dopicar as the first morning dose, after a night without any levodopa. The daily dosage of Dopicar chosen should provide approximately 25% of the previous levodopa daily dosage.

The suggested starting dosage for most patients is one tablet of Dopicar, 3 or 4 times a day.

Patients who require less than 1,500 mg levodopa a day should be started on half tablet of Dopicar, 3 or 4 times a day. Adjustment in dosage may be made as necessary, by adding or omitting half-one tablet a day.

Maintenance

Experience with a total daily dosage greater than 200 mg carbidopa is limited.

If general anesthesia is required, therapy with Dopicar may be continued as long as the patient is permitted to take fluids and medication orally. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Patients receiving levodopa with another decarboxylase inhibitor

When transferring a patient to Dopicar from levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours (for instant release formulations) or 24 hours (for sustained release formulations) before Dopicar is started. Begin with a dosage of Dopicar that will provide the same amount of levodopa as contained in the other levodopa/decarboxylase inhibitor combination.

Patients receiving other antiparkinsonian agents

Current evidence indicates that other antiparkinsonian agents may be continued when Dopicar is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

Paediatric population

The safety of Dopicar in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

Elderly

There is wide experience in the use of this product in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

Method of administration

To be taken orally.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Dopicar. These inhibitors must be discontinued at least two weeks before starting Dopicar. Dopicar may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride). (see section 4.5 'Interaction with other medicinal products and other forms of interaction'.)
- Dopicar is contraindicated in patients with narrow-angle glaucoma.
- Since levodopa may activate a malignant melanoma, it should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.
- Use in patients with severe psychoses.

See also section 4.6 'Pregnancy and lactation'.

4.4 Special warnings and precautions for use

- Dopicar is not recommended for the treatment of drug-induced extrapyramidal reactions.
- 'Dopicar should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastrointestinal haemorrhage).
- Care should be exercised when Dopicar is administered to patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.
- Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.
- All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with current psychoses should be treated with caution.
- Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.
- As with levodopa, Dopicar may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone should be observed carefully when Dopicar is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Dopicar may cause a recurrence. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Therefore, any abrupt dosage reduction or withdrawal of Dopicar should be carefully observed, particularly in patients who are also receiving neuroleptics.

- Concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect. Patients with a history of convulsions should be treated with caution.
- As with levodopa, periodic evaluation of hepatic, haematopoetic, cardiovascular and renal function are recommended during extended therapy.
- Patients with chronic wide-angle glaucoma may be treated cautiously with Dopicar, provided the intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.
- If general anaesthesia is required, therapy with Dopicar may be continued for as long as the patient is permitted to take fluids and medication by mouth. If therapy has to be stopped temporarily, Dopicar may be restarted as soon as oral medication can be taken at the same daily dosage as before.
- Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as drugs used to treat Parkinson's disease. Therefore, patients and providers are advised to monitor for melanomas on a regular basis when using Dopicar for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Laboratory Tests

- Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Dopicar than with levodopa. Transient abnormalities include elevated levels of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase.
- Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported.
- Positive Coombs' tests have been reported, both with Dopicar and levodopa alone.
- 'Dopicar may cause a false positive result when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine. The use of glucose oxidase methods may give false negative results for glycosuria.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Dopicar. Review of treatment is recommended if such symptoms develop.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with Dopicar.

Antihypertensive agents

Postural hypotension can occur when Dopicar is added to the treatment of patients already receiving antihypertensive drugs. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants. (see first paragraph of section 4.3 'Contraindications' for patients receiving MAOIs).

Anticholinergics
Anticholinergics may affect the absorption and thus the patient's response.

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

Other drugs
- To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian drugs.
- Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, and risperidone) and isoniazid, may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with Dopicaer should be carefully observed for loss of therapeutic response.
- Use of Dopicar with dopamine-depleting agents (e.g., tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.
- Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see section 4.3 'Contraindications')
- Since levodopa competes with certain amino acids, the absorption of Dopicar may be impaired in some patients on a high protein diet.
- The effect of simultaneous administration of antacids with Dopicar on the bioavailability of levodopa has not been studied.
- Dopicar may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.6 Pregnancy and lactation

Pregnancy
Although the effects of Dopicar on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Therefore, the use of Dopicar in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Breast-feeding
It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue the use of Dopicar, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary and certain side effects that have been reported with Dopicar may affect some patients' ability to drive or operate machinery. Patients treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or

death (e.g. operating machines), until such recurrent episodes and somnolence have resolved (see also section 4.4 ‘Special warnings and precautions for use’).

4.8 Undesirable effects

Side effects that occur frequently with Dopicar are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are dyskinesias including choreiform, dystonic and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Other side effects reported in clinical trials or in post-marketing experience include:

Infections and infestations: urinary tract infections (frequency: very common)

Body as a whole: syncope, chest pain, anorexia.

Cardiovascular: cardiac irregularities and/or palpitations, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastrointestinal: vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva.

Haemotologic: leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome (see section 4.3 ‘Contraindications’), bradykinetic episodes (the “on-off” phenomenon), dizziness, paraesthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory: dyspnoea.

Skin: alopecia, rash, dark sweat.

Urogenital: dark urine.

Rarely convulsions have occurred; however, a causal relationship with Dopicar has not been established.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with Dopicar include:

Gastrointestinal: dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of the tongue.

Metabolic: weight gain or loss, oedema.

Nervous System/Psychiatric: asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramp, trismus, activation of latent Horner’s syndrome, insomnia, anxiety, euphoria, falling, gait abnormalities and Dopamine Dysregulation Syndrome.

Description of selected adverse reactions

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Impulse control disorders

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

Skin: flushing, increased sweating.

Special senses: diplopia, blurred vision, dilated pupils, oculogyric crises.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see section 4.3 'Contraindications').

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Treatment
Management of acute overdosage with Dopicar is basically the same as management of acute overdosage with levodopa; however pyridoxine is not effective in reversing the actions of Dopicar. ECG monitoring should be instituted, and the patient carefully observed for the possible development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given.
The possibility that the patient may have taken other drugs as well as Dopicar should be taken into consideration. To date, no experience has been reported with dialysis, and hence its value in the treatment of overdosage is not known.

The terminal half-life of levodopa is about two hours in the presence of carbidopa.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiparkinsonian agent
ATC code: N04BA02

Mechanism of action

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.

Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of side effects.

Pharmacodynamics effects

Dopicar is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson's disease and syndrome.

When response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of Dopicar usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, Dopicar permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

5.2 Pharmacokinetic properties

Absorption
Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal tract. It has a plasma half life of about 1 hour and is mainly converted

by decarboxylation to dopamine, a proportion of which is converted to noradrenaline. Up to 30 % is converted to 3-O-methyldopa which has a half life of 9 to 22 hours. About 80 % of levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and dihydroxyphenylactic acid. Less than 1 % is excreted unchanged.

Once in the circulation it competes with other neutral amino acids for transport across the blood brain barrier. Once it has entered the striatal neurones it is decarboxylated to dopamine, stored and released from presynaptic neurones. Because levodopa is so rapidly decarboxylated in the gastrointestinal tract and the liver, very little unchanged drug is available for transport into the brain. The peripheral decarboxylation reduces the therapeutic effectiveness of levodopa but is responsible for many of its side effects. For this reason levodopa is usually administered together with a peripheral decarboxylase inhibitor such as carbidopa, so that lower doses may be given to achieve the same therapeutic effect.

Carbidopa in the absence of levodopa, is rapidly but incompletely absorbed from the gastrointestinal tract following oral dosing. Following an oral dose approximately 50 % is recorded in the urine, with about 3 % of this as unchanged drug. It does not cross the blood brain barrier but crosses the placenta and is excreted in breast milk. Turnover of the drug is rapid and virtually all unchanged drug appears in the urine within 7 hours.

Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine but as it does not cross the blood brain barrier, effective brain levels of dopamine get produced with lower levels of levodopa therapy reducing the peripheral side effects, noticeably nausea and vomiting and cardiac arrhythmias.

5.3. Pre-clinical Safety Data

Dopicar is well established in medical use. Preclinical data is broadly consistent with clinical experience. (For reproductive toxicity , see section 4.6 Pregnancy and Lactation).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, pregelatinised starch, starch, magnesium stearate, FD&C Blue No. 2.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

The product may be used up to 60 days after first opening of the bottle, but no later than the expiry date.

6.4 Special precautions for storage

Store in a dry place below 25°C.

6.5 Nature and contents of container

HDPE bottle containing 30 tablets.

6.6 Instructions for Use, Handling and Disposal

Not applicable.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.
124 Dvora HaNevi'a St., Tel Aviv 6944020 Israel

8. REGISTRATION NUMBER(S)

040.96.22970

The leaflet was revised in December 2023 accroding to MOHs guidelines

תאריך הגשת העלון	פרקים שהתעדכנו	רפרנס לעדכון (שם עלון רפרנס/הנחיית מ.ב.)	הערות
02.2019	עדכון כללי בהתאם לעלון אסמכתא ונוהל הגשה ועדכון עלונים מתאריך 01.01.2018	SINEMET® 25 mg/250 mg Tablets, SPC (Merck Sharp & Dohme Limited), UK, 16/01/2019	הגשה במסלול סרטיפיקציה העלון לא אושר
07/2021	- עדכון העלון כולל החמרות בסעיפים 4.4 ו- 4.8 - עדכון פורמט, דיווח תופעות לוואי, הוספת חיי מדף וכו'	SINEMET® 25 mg/250 mg Tablets, SPC, Organon Pharma Limited (MSD), UK, 26/04/2021 נוהל ופורמט משרד הבריאות 01.01.2018	הגשה במסלול נוטיפיקציה לפי הנחיות משרד הבריאות לעדכון עבור תכשיר זה.
01/2022	- <u>עדכון סעיף 4.4 - TYPO</u> <u>- עדכון סעיף 7 (שם בעל רישום וכתובתו)</u>	<u>בקשה מרוכזת לשינוי שהוגשה למחלקה לרישום</u>	שנויים שלא דורשים אישור, בהמשך להגשת העלון בנוטיפיקציה.
12/2023	- עדכון העלון כולל החמרות בסעיף 4.8 -	SINEMET® 25 mg/250 mg Tablets, SPC, Organon Pharma Limited (MSD), UK, 10/10/2023	הגשה במסלול נוטיפיקציה עדכון Prac ב- EMA