PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**AG-Levocarb**

Levodopa and Carbidopa Tablets

Tablets, 100 mg / 10 mg, 100 mg / 25 mg, 250 mg / 25 mg (levodopa / carbidopa), Oral

USP

Antiparkinson Agent

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AG-Levocarb (levodopa and carbidopa tablets) is indicated for the treatment of Parkinson's disease.

AG-Levocarb is not recommended for the treatment of drug-induced extrapyramidal reactions.

1.1 Pediatrics

Pediatrics (< 18 years of age):
The safety and effectiveness of levodopa and carbidopa in patients under 18 years of age has not been established.

1.2 Geriatrics

Not applicable.

2 CONTRAINDICATIONS

- AG-Levocarb is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING of the product monograph.

- Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with AG-Levocarb. These inhibitors must be discontinued at least two weeks prior to initiating therapy with AG-Levocarb. AG-Levocarb may be administered concomitantly with a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl) (see 9 DRUG INTERACTIONS, Drug-Drug Interactions, Psychoactive Drugs) at the manufacturer's recommended dose which maintains selectivity for MAO type B.

- AG-Levocarb should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

- As with levodopa, AG-Levocarb should not be given when administration of a sympathomimetic amine is contraindicated (e.g., epinephrine, norepinephrine or isoproterenol).

- Because levodopa may activate a malignant melanoma, AG-Levocarb should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Sudden Onset of Sleep**

Patients receiving treatment with levodopa and carbidopa tablets and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including the driving of a car, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on levodopa and carbidopa tablets, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with AG-Levocarb such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking AG-Levocarb. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician.

Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Currently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness**.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with AG-Levocarb (levodopa and carbidopa tablets) must be individualized

and drug administration must be continuously matched to the needs and tolerance of the patient. It should be borne in mind that the therapeutic range of AG-Levocarb is narrower than that of levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and the dosage ranges recommended should usually not be exceeded. The appearance of involuntary movements should be regarded as a sign of levodopa toxicity and as an indication of overdosage, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias.

- **If a patient being treated with levodopa is switched to therapy with AG-Levocarb, levodopa must be discontinued at least twelve hours or more before therapy with AG-Levocarb is initiated.**

- Although the administration of carbidopa permits control of Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at lower dosages and sooner during therapy with AG-Levocarb than with levodopa.

- AG-Levocarb tablets are available in a 4:1 ratio (AG-Levocarb 100 mg / 25 mg) and in a 10:1 ratio of levodopa to carbidopa (AG-Levocarb 100 mg / 10 mg and 250 mg / 25 mg). Tablets of the two ratios may be given separately or combined as needed to provide the optimal dosage.

- Dividing the tablets along the score line may not give exact equal half doses.

- Studies have shown that peripheral dopa decarboxylase is saturated by carbidopa at doses between 70 to 150 mg per day. Patients receiving less than 70 mg per day of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

- For patients who require only low doses of levodopa, e.g., less than 700 mg, AG-Levocarb 100 mg / 25 mg may be helpful.

4.2 Recommended Dose and Dosage Adjustment

- **Induction of Therapy in Patients Not Receiving Levodopa**

Dosage is best initiated with one tablet of AG-Levocarb 100 mg / 25 mg three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be carefully increased by one tablet every three days until the optimal dosage has been reached

which does not produce dyskinesias.

While increasing the dosage during the induction period, the doses should be divided, aiming at a frequency of dosing of at least four times a day. If further titration is necessary after a daily dosage level of six tablets of AG-Levocarb 100 mg / 25 mg has been reached, tablets of AG-Levocarb 100 mg / 10 mg or 250 mg / 25 mg may be used as needed to provide the optimal dosage.

Usually no patient should receive more than 1500 mg of levodopa a day. Some patients, including those with postencephalitic parkinsonism, are more sensitive to levodopa and require specially careful dosage adjustment.

- **Induction of Therapy in Patient Receiving Levodopa**
  Levodopa must be discontinued at least twelve hours or more before AG-Levocarb is started. A dosage of AG-Levocarb should be used that will provide approximately 20% of the previous levodopa daily dosage; this can be started in the morning after the day in which the treatment with levodopa has been stopped. For example, if a patient is receiving 4,000 mg of levodopa per day, the dosage of AG-Levocarb should not provide more than 750 mg of levodopa per day divided into four to six doses.

  AG-Levocarb 100 mg / 25 mg tablets should be used to start medication for patients requiring lower dosages of levodopa.

- **Adjustment and Maintenance of Therapy**
  Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one tablet of AG-Levocarb 100 mg / 25 mg may be substituted for each tablet of AG-Levocarb 100 mg / 10 mg. When more levodopa is required, AG-Levocarb 250 mg / 25 mg should be substituted for AG-Levocarb 100 mg / 25 mg or 100 mg / 10 mg. If necessary, the dosage of AG-Levocarb 250 / 25 may be increased by one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

  Because both therapeutic and adverse responses occur more rapidly with levodopa and carbidopa than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with levodopa and carbidopa 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.

  Current evidence indicates that other standard antiparkinsonian drugs may be continued while levodopa and carbidopa tablets are being administered although their

dosage may have to be adjusted.

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

4.3 Reconstitution

- Not Applicable.

4.4 Administration

- Not Applicable.

4.5 Missed Dose

If a tablet is missed, it should be taken as soon as possible. If it is almost time to take the next tablet, the missed tablet should not be taken, and the normal schedule should be resumed.

5 OVERDOSAGE

Management of acute overdosage with AG-Levocarb (levodopa and carbidopa tablets) is basically the same as management of acute overdosage with levodopa alone. However, pyridoxine is not effective in reversing the actions of AG-Levocarb.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the possible development of arrhythmias; if required, appropriate antiarrhythmic the rapy should be given. The possibility that the patient may have taken other drugs as well as AG-Levocarb should be taken into consideration. To date, no experience has been reported with dialysis, hence, its value in overdosage is not known.

For up-to-date information on the management of a suspected drug overdose, the physician should consider contacting a regional Poison Control Centre.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	tablet 100 mg / 10 mg, 100 mg / 25 mg, 250 mg / 25 mg	crospovidone, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

Description

AG-Levocarb 100 mg / 10 mg: Each blue, oval, biconvex tablet, debossed with "J" & "P" on either side of scoreline on one side and the other side debossed with "10/100", contains 100 mg of levodopa and 10 mg of carbidopa. Available in HDPE bottles of 100 tablets.

AG-Levocarb 100 mg / 25 mg: Each yellow, oval, biconvex tablet, debossed with "J" & "P" on either side of scoreline on one side and the other side debossed with "25/100", contains 100 mg of levodopa and 25 mg of carbidopa. Available in HDPE bottles of 100 and 500 tablets.

AG-Levocarb 250 mg / 25 mg: Each blue, oval, biconvex tablet, debossed with "J" & "P" on either side of scoreline on one side and the other side debossed with "25/250'', contains 250 mg of levodopa and 25 mg of carbidopa. Available in HDPE bottles of 100 and 500 tablets.

AG-Levocarb 100 mg / 10 mg and 250 mg / 25 mg tablets also contain Indigotine AL Lake and Brilliant blue FCF lake. AG-Levocarb 100 mg / 25 mg tablets contain D&C Yellow No. 10 lake.

7 WARNINGS AND PRECAUTIONS

General

When patients already receiving levodopa are switched to AG-Levocarb, levodopa must be discontinued for at least 12 hours or more before AG-Levocarb is started. AG-Levocarb should be substituted at a dosage that will provide approximately 20% of the previous levodopa dosage (see 4 DOSAGE AND ADMINISTRATION).

Patients who are taking AG-Levocarb should be instructed not to take additional levodopa unless it is prescribed by the physician.

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are

recommended during extended therapy with AG-Levocarb (levodopa and carbidopa tablets).

Physical Activity:
Patients who improve while on therapy with AG-Levocarb should increase physical activities gradually, with caution, consistent with other medical considerations such as the presence of osteoporosis or phlebothrombosis.

Cardiovascular
Care should be exercised in administering AG-Levocarb to patients with a history of myocardial infarction or who have atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment in a facility with provisions for intensive cardiac care.

Gastrointestinal
AG-Levocarb should be administered cautiously to patients with a history of peptic ulcer disease due to the possibility of upper gastrointestinal hemorrhage.

Neurologic
The levodopa induced involuntary movements and 'on and off' phenomenon may appear earlier with combination therapy.

As with levodopa, AG-Levocarb may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. Because carbidopa permits more levodopa to reach the brain and thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with AG-Levocarb than with levodopa. The occurrence of dyskinesias may require dosage reduction.

AG-Levocarb should be used cautiously in patients who have a history of seizures or have conditions associated with seizure or have a lowered seizure threshold.

Neuroleptic Malignant Syndrome: A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, altered consciousness, mental changes, autonomic instability and increased serum creatine phosphokinase has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. Therefore, patients should be observed carefully when the dosage of AG-Levocarb is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Psychomotor Performance: Certain side effects that have been reported with levodopa and carbidopa tablets may affect some patients' ability to drive or operate machinery.

Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous

machinery, including driving motor vehicles, while taking AG-Levocarb. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician (see 7 WARNINGS AND PRECAUTIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Sudden Onset of Sleep).

Ophthalmologic

Use in Patients with Glaucoma: Pupillary dilatation and activation of latent Horner's syndrome have been reported during levodopa treatment. Patients with chronic wide angle glaucoma should therefore be treated cautiously with AG-Levocarb. The intraocular pressure should be well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Peri-Operative Considerations

If general anesthesia is required, therapy with AG-Levocarb may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication (see 4 DOSAGE AND ADMINISTRATION, Adjustment and Maintenance of Therapy).

Psychiatric

Patients should be monitored carefully for the development of depression with suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Behavioural Changes: Patients and caregivers should be advised to adhere to dosage instructions given by the physician. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioral symptoms of impulse control disorders, including pathological (compulsive) gambling, hypersexuality, increased libido, compulsive spending/buying, and binge/compulsive eating, have been reported in patients treated with dopaminergic agonists and/or other dopaminergic treatments for Parkinson's disease, including levodopa and carbidopa (see 8 ADVERSE REACTIONS). Literature and postmarketing reports have described a very rare addictive pattern of dopamine replacement therapy, in which patients use doses in excess of those required to control their motor symptoms. Review of treatment is recommended if such symptoms develop.

Hallucinations: Hallucinations and confusion are known side effects of treatment with dopaminergic agents, including levodopa. Patients should be aware of the fact that hallucinations (mostly visual) can occur.

Skin

Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other

factors, such as drugs used to treat Parkinson's disease, is unclear. For the reasons stated above, patients and healthcare providers are advised to monitor for melanomas frequently and on a regular basis when using AG-Levocarb for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

7.1 Special Populations

7.1.1 Pregnant Women

Although the effects of AG-Levocarb on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see 16 NON-CLINICALTOXICOLOGY, Teratologic and Reproductive Studies). Therefore, use of AG-Levocarb in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to the mother and to the fetus.

7.1.2 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 breast milk was reported. AG-Levocarb should not be given to nursing mothers unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety of levodopa and carbidopa in patients under 18 years of age has not been established.

Monitoring and Laboratory Tests

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy with AG-Levocarb (levodopa and carbidopa tablets).

AG-Levocarb may cause a false-positive reaction for urinary ketone bodies when a tape test is used for determination of ketonuria. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or levodopa/carbidopa therapy (see 9 DRUG INTERACTIONS, Drug-Laboratory Test Interactions)

7.1.4 Geriatrics

Not applicable.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most common serious adverse reactions occurring with levodopa and carbidopa are dyskinesias, including choreiform, dystonic and other involuntary movements, and nausea. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with levodopa and carbidopa has not been established.

Other adverse reactions reported in clinical trials or in post-marketing experience include:

Body as a whole:

Syncope, chest pain, anorexia, asthenia.

Cardiovascular:

Cardiac irregularities and/or palpitation, hypotension, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastrointestinal:

Vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhea, dark saliva, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic:

Leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Hypersensitivity:

Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal:

Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric:

Neuroleptic malignant syndrome (see 7 WARNINGS AND PRECAUTIONS), bradykinetic episodes (the "on-off" phenomenon), dizziness, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes, paresthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, dream abnormalities including nightmares, insomnia, headache, depression with or without development of suicidal tendencies, dementia, agitation, confusion.

In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine agonists and/or other dopaminergic treatments, and rarely in patients treated with levodopa, including levodopa and carbidopa (see 7 WARNINGS AND PRECAUTIONS).

Respiratory:

Dyspnea, upper respiratory infection.

Skin:

Alopecia, rash, increased sweating, dark sweat, malignant melanoma (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Skin).

Urogenital:

Dark urine, urinary frequency, urinary tract infection.

Other adverse reactions that have been reported with levodopa alone and with various levodopa carbidopa formulations, and may occur with AG-Levocarb are:

Body as a whole:

Fatigue.

Cardiovascular:

Myocardial infarction.

Gastrointestinal:

Sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, flatulence, burning sensation of tongue, gastrointestinal pain, heart burn.

Metabolic:

Weight gain or loss, edema.

Musculoskeletal:

Leg pain.

Nervous System/Psychiatric:

Decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome, anxiety, euphoria, falling and gait abnormalities, extrapyramidal disorder, nervousness, memory impairment, peripheral neuropathy.

Respiratory:

Pharyngeal pain, cough.

Skin:

Flushing.

Special Senses:

Diplopia, blurred vision, dilated pupils, and oculogyric crises.

Urogenital:

Urinary retention, urinary incontinence, priapism.

Miscellaneous:

Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, creatinine, uric acid, and positive Coomb's test.

Decreased hemoglobin and hematocrit; elevated serum glucose; and white blood cells, bacteria and blood in the urine have been reported.

Decreased white blood cell count and serum potassium; protein and glucose in urine have been reported with levodopa alone and with various levodopa-carbidopa formulations, and may occur with AG-Levocarb.

8.5 Post-Market Adverse Reactions

Information is found with clinical trial adverse drug reactions under Subsection 8.2.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Caution is advised when AG-Levocarb is used with other concomitant medications to avoid drug interactions.

9.2 Drug-Behavioural Interactions

See 7 WARNINGS AND PRECAUTIONS, Psychiatric, Behavioural Changes.

9.3 Drug-Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with AG-Levocarb:

Antihypertensive Drugs: Symptomatic postural hypotension can occur when AG-Levocarb are added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with AG-Levocarb is started, dosage adjustment of the antihypertensive drug may be required.

Psychoactive Drugs: Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones and risperidone) 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 AG-Levocarb should be carefully observed for loss of antiparkinsonian effect.

Concomitant therapy with selegiline and levodopa-carbidopa preparations may be associated with severe orthostatic hypotension not attributable to levodopa-carbidopa alone (see 2 CONTRAINDICATIONS).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and levodopa and carbidopa tablets. (For patients receiving monoamine oxidase inhibitors, see 2 CONTRAINDICATIONS).

Dopamine Depleting Agents: Use of AG-Levocarb with dopamine-depleting agents (e.g. reserpine[1] and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended as reduction in patient response to levodopa may occur.

Isoniazid: Isoniazid may reduce the therapeutic effects of levodopa.

Anesthetics: When general anesthesia is required, AG-Levocarb should be discontinued the night before. Therapy with AG-Levocarb may be continued as soon as the patient is able to take medication by mouth.

Iron: Studies have demonstrated that ferrous sulphate decreases the bioavailability of carbidopa and/or levodopa. Because this interaction may be due to the formation of drug-iron complexes, other iron supplement formulations and iron-containing multivitamins may have similar effects.

Metoclopramide: Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

9.4 Drug-Food Interactions

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

9.5 Drug-Herb Interactions

Not applicable.

9.6 Drug-Laboratory Test Interactions

AG-Levocarb may cause a false-positive reaction for urinary ketone bodies when a tape test is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients with levodopa-carbidopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or levodopa-carbidopa therapy.

[1] *Not marketed in Canada*

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease.

10.2 Pharmacodynamics

When levodopa is administered orally it is rapidly converted to dopamine by decarboxylation in peripheral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in peripheral tissues.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to peripheral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. Combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit by about 75 to 80%, permits an earlier response to therapy, and also reduces the incidence of nausea, vomiting and cardiac arrhythmias. Combined therapy, however, does not decrease adverse reactions due to central effects of levodopa.

10.3 Pharmacokinetics

At steady state, the bioavailability of carbidopa from carbidopa and levodopa tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa. Since levodopa competes with certain aminoacids, the absorption of levodopa may be impaired in some patients on a high protein diet.

Following simultaneous administration of carbidopa and levodopa in man, both plasma levels and plasma half-life of levodopa are markedly increased over those found when the same dosage of levodopa is given alone, while plasma levels of dopamine and homovanillic acid are reduced or do not change. Nevertheless, the plasma levels vary greatly between patients. The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa

produced greater urinary excretion of levodopa in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature, 15-30°C, in a well-closed bottle. Protect from light and moisture.

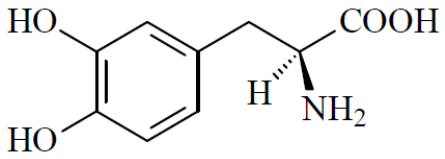
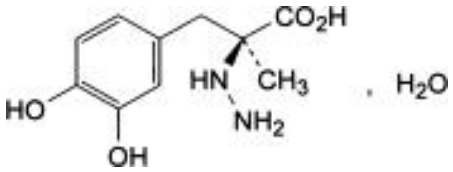
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Levodopa and	Carbidopa
Chemical Name:	(2S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid	(2S)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate
Molecular Formula:	$C_9H_{11}NO_4$	$C_{10}H_{14}N_2O_4 \cdot H_2O$
Molecular Mass:	197.2 g/mol	244.2 g/mol
	Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3 g/mol	
Structural Formula:		
Physicochemical Properties:	White or almost white, crystalline powder; slightly soluble in water, practically insoluble in ethanol (96 percent), it is freely soluble in 1M hydrochloric acid and sparingly soluble in 0.1M hydrochloric acid.	White or yellowish-white powder; slightly soluble in water, very slightly soluble in ethanol (96 percent), practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Not applicable.

14.2 Study Results

Not applicable.

14.3 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, single-dose (1 x 100 mg/25 mg), crossover, oral bioequivalence study of [Pr]AG-Levocarb (Angita Pharma Inc.) and [Pr]APO-LEVOCARB (Apotex Inc.), was conducted in healthy, adult, human subjects under fasting conditions. A summary of the bioavailability data from the 59 subjects who completed the study is presented in the following tables**.**

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levodopa (1 x 100 mg Levodopa / 25 mg carbidopa) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	2161.42 2203.76 (20.41)	2278.59 2329.15 (21.33)	94.9	92.4 - 97.4
AUC_I (ng.h/mL)	2198.88 2240.50 (20.07)	2313.33 2363.53 (21.08)	95.1	92.7 - 97.5
C_{max} (ng/mL)	1166.26 1239.33 (37.12)	1156.54 1209.33 (30.71)	100.8	93.2 - 109.1
T_{max}[3] (h)	0.75 (0.25-2.33)	1.00 (0.25 - 3.00)		
$T_{½}$[4] (h)	1.78 (10.54)	1.80 (12.06)		

[1] [Pr]AG-Levocarb (levodopa/carbidopa) tablets, 100 mg/25 mg (Angita Pharma Inc.)
[2] [Pr]APO-LEVOCARB (levodopa/carbidopa) tablets, 100 mg/25 mg (Apotex Inc.)
[3] Expressed as the median (range) only.
[4] Expressed as the arithmetic mean (CV %) only.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Carbidopa (1 x 100 mg levodopa / 25 mg carbidopa) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	273.21 289.53 (34.19)	273.38 290.74 (33.31)	99.9	91.8 - 108.8
AUC_I (ng.h/mL)	280.95 296.86 (33.45)	280.60 297.70 (32.89)	100.1	92.2 - 108.7
C_{max} (ng/mL)	76.48 81.67 (37.98)	75.34 81.51 (38.30)	101.5	92.2 - 111.8
T_{max}[3] (h)	1.75 (0.75 - 4.50)	2.33 (0.75 - 5.00)		
$T_{½}$[4] (h)	1.78 (26.08)	1.73 (22.62)		

[1] [Pr]AG-Levocarb (levodopa/carbidopa) tablets, 100 mg/25 mg (Angita Pharma Inc.)

[2] [Pr]APO-LEVOCARB (levodopa/carbidopa) tablets, 100 mg/25 mg (Apotex Inc.)

[3] Expressed as the median (range) only.

[4] Expressed as the arithmetic mean (CV %) only.

A randomized, two-treatment, two-period, single-dose (1 x 250 mg/25 mg), crossover, oral bioequivalence study of [Pr]AG-Levocarb (Angita Pharma Inc.) and [Pr]APO-LEVOCARB (Apotex Inc.), was conducted in healthy, adult, human subjects under fasting conditions. A summary of the bioavailability data from the 54 subjects who completed the study is presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levodopa (1 x 250 mg levodopa /25 mg carbidopa) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	5811.46 5880.22 (16.25)	6261.55 6348.57 (17.23)	92.8	90.6-95.1
AUC_I (ng.h/mL)	5849.86 5918.64 (16.18)	6300.31 6387.37 (17.18)	92.9	90.6-95.1
C_{max} (ng/mL)	2655.00 2780.17 (32.95)	2662.23 2753.35 (27.63)	99.7	93.5-106.4
T_{max}[3] (h)	0.75 (0.25-2.67)	1.25 (0.25-3.67)		
$T_{½}$[4] (h)	1.63 (11.42)	1.58 (9.52)		

[1] [Pr]AG-Levocarb (levodopa/carbidopa) tablets, 250 mg/25 mg (Angita Pharma Inc.)

[2] [Pr]APO-LEVOCARB (levodopa/carbidopa) tablets, 250 mg/25 mg (Apotex Inc.)

[3] Expressed as the median (range) only.

[4] Expressed as the arithmetic mean (CV %) only.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Carbidopa tablets (1 x 250 mg levodopa / 25 mg carbidopa) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	288.72 310.47 (39.82)	311.67 332.45 (36.20)	92.6	85.2-100.7
AUC_I (ng.h/mL)	295.98 317.39 (39.15)	319.33 339.67 (35.56)	92.7	85.4-100.6
C_{max} (ng/mL)	74.32 81.94 (50.40)	79.64 86.70 (41.75)	93.3	85.6-101.8
T_{max}[3] (h)	2.67 (0.75-5.00)	2.17 (0.75-4.50)		
$T_{½}$[4] (h)	1.71 (29.57)	1.69 (22.68)		

[1] PrAG-Levocarb (levodopa/carbidopa) tablets, 250 mg/25 mg (Angita Pharma Inc.)
[2] PrAPO-LEVOCARB (levodopa/carbidopa) tablets, 250 mg/25 mg (Apotex Inc.)
[3] Expressed as the median (range) only.
[4] Expressed as the arithmetic mean (CV %) only

14.4 Immunogenicity

Not applicable.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:
Summary of Acute Oral Toxicity Data

A. Carbidopa

Species	Sex	LD_{50} mg/kg	Signs of Toxicity

Rat (A&W)	F	4810	Ptosis, ataxia, decreased activity
Rat (A&W)	M	5610	
Rat (I)	M&F	2251	
Mouse (A)	F	1750	As above plus bradypnea

B. Levodopa

Species	Sex	LD_{50} mg/kg	Signs of Toxicity
Rat (A)	F	2260	Vocalization, irritability, excitability, increased activity followed by decreased activity.
Rat (A)	M	1780	
Mouse	F	1460	

C. Carbidopa/Levodopa (1:1)

Species	Sex	LD_{50} mg/kg	Signs of Toxicity
Mouse	M&F	1930[xx]	Erect tail, piloerection, ataxia, lacrimation, increased activity and irritability, clonic convulsion.

D. Carbidopa/Levodopa (1:3)

Species	Sex	LD_{50} mg/kg	Signs of Toxicity
Mouse	M&F	3270[xx]	As above

[xx] Sum of individual doses of carbidopa/levodopa
A – Adult
W – Weanling
I – Infant

The preceding table summarizes the acute toxicity data for carbidopa and levodopa alone and in combination. Mortality usually occurred in 12 hours with carbidopa and 30 minutes with levodopa. With the combination of carbidopa and levodopa, deaths occurred between 30 minutes and 24 hours at high doses and up to 12 days with lower doses. The toxicity did not continue to decrease with drug ratios above 1:3.

In oral subacute toxicity studies, carbidopa is more toxic for dogs than for monkeys or rats. Following doses of 45 mg/kg/day for six weeks, dogs exhibited anorexia, emesis, tarry stools, diarrhea, dry nose and/or gums, fine muscular tremors, weight loss, prolonged clotting and

prothrombin times, bilirubinuria and decreases in total leukocytes, total protein and albumin, and SGOT activity. The increased toxicity in dogs appeared to be due to pyridoxine-deficiency, since concurrent administration of pyridoxine decreased the toxicity of carbidopa. Doses up to 135 mg/kg/day produced no drug-related effects in the monkey and only flaccidity in some rats. Slight centrolobular vacuolization of hepatocytes in two rats and significantly higher mean kidney weights were observed in the highest dosage group.

Oral toxicity studies with doses of levodopa up to 1000 mg/kg/day for 13 weeks indicated no treatment-related effects in monkeys. In rats, treatment-related morphologic changes occurred in salivary glands (hypertrophy of acinar cells) and adrenals (cytoplasmic rarefaction of the zona glomerulosa) at all dosage levels, in kidneys of rats receiving 500 and 1000 mg/kg/day (tubular necrosis with regeneration and necrosis respectively) and in the stomach (focal necrosis of the superficial epithelium) of some rats in the high dosage group. A statistically significant leucocytosis and increase in heart and kidney weights occurred in females of this latter group; males had a significant increase in heart and liver weights and a decrease in growth rate. Clinical signs of toxicity included ptyalism, piloerection, hyperventilation with intermittent dyspnea and decreased activity.

Combinations of carbidopa and levodopa in respective doses of 30/30, 30/60 and 30/120 mg/kg/day were given orally for 14 weeks to monkeys and for 13 weeks to rats. Signs of toxicity in monkeys were related to dosage and indicated that coadministration enhanced the pharmacologic activity of levodopa. In the rat, the apparent degree of potentiation of levodopa by carbidopa appeared to be less.

Three dosage ratios of carbidopa and levodopa were given orally to monkeys and rats for 54 weeks. Dosages of 10/20 mg/kg/day had no apparent physical effects while hyperactivity occurred in monkeys at dosages of 10/50 and 10/100 mg/kg/day, and continued for 32 weeks with the higher dose. Muscular incoordination and weakness were observed until the twenty-second week with the 10/100 mg/kg/day dose. Pathologic studies did not show any morphologic changes. Rats that received 10/50 and 10/100 mg/kg/day had a decrease in normal activity and displayed abnormal body positions. The higher dose caused excessive salivation. There was a decrease in body weight gain. Morphological changes, where present, were those noted with levodopa alone.

Acute oral interaction studies in mice demonstrated that pre-treatment with pharmacological doses (1 mg/kg) of benztropine mesylate or trihexyphenidyl hydrochloride did not affect the acute toxicity of carbidopa, levodopa or a 1:3 mixture of carbidopa:levodopa.

Higher doses (24 to 184 mg/kg) increased the acute toxicity of carbidopa and the combination but not of levodopa. Pre-treatment with an MAO inhibitor (phenelzine) resulted in a five-fold increase in acute toxicity of the mixture and a four-fold increase in toxicity of levodopa with no change in toxicity of carbidopa. Synergism between a 1:10 mixture of carbidopa:levodopa and amantadine was indicated by increased toxicity in the female mouse. However, no synergism

was demonstrated between therapeutic doses of amantadine and carbidopa, levodopa or a 1:10 mixture.

Reproductive and Developmental Toxicology:

Teratologic and Reproductive Studies

The incidences of malformations of the heart and great vessels were 0 of 105, 1 of 94, and 6 of 81 fetuses from rabbits given 75, 125 or 250 mg of levodopa/kg/day respectively by the oral route, indicating a dose-dependent teratogenic effect. Anomalies included septal defects, constricted or missing ductus arteriosus, enlarged aortic arches, fused aortas and pulmonary arches, and transpositions.

The same types of malformations were also induced in fetuses from rabbits given doses of various combinations of levodopa and carbidopa, but they were not observed when carbidopa was given alone. The malformations, possibly drug-related, were also seen in one mouse fetus from a dam which had received 500 mg of levodopa/kg/day. No drug-induced malformations were observed in fetuses of mice given various combinations of the two drugs or in the offspring of rats given carbidopa. The significance of heart and great vessel malformations in one stunted fetus from a female mouse given the lowest dose of carbidopa (30 mg/kg/day) and in one stillborn pup from a female rat given the mid-dose of the drug combination (10 mg of carbidopa/kg plus 50 mg of levodopa/kg/day) is questionable; both offspring also had other external, cranial and skeletal malformations.

Other effects on reproduction associated with combination treatments in the rabbit included decreased maternal weight gains and fetal weights, and increased resorptions, and incidences of various skeletal anomalies, especially of vertebral centra and skull bones. In mice given the combination product, only a decrease in fetal weight occurred. In rats, none of these effects were observed; the maximal dose administered was 10 mg of carbidopa/kg plus 100 mg of levodopa/kg/day.

DETAILED PHARMACOLOGY

Levodopa: Pharmacological experiments in various species of animals have shown that levodopa produced increased motor activity, aggressive behaviour and electroencephalographic alerting behaviour. However, occasional sedation and ataxia have also been reported in some animal species. Levodopa also reverses the reserpine induced Parkinson-like effects in animals. Cardiovascular studies in dogs and cats have shown that levodopa increases the catecholamine levels in the brain which has been evident in an initial increase in blood pressure followed by a secondary decrease in blood pressure. The changes in blood pressure appear to correlate with the changes in renal function. Biochemical studies *in vivo* as well as *in vitro* have demonstrated that levodopa is decarboxylated to dopamine in many tissues. Levodopa crosses the blood-brain barrier and elevates the dopamine concentration in the brain. The dopamine formed can be degraded to dihydroxyphenylacetic and homovanillic acids which are the two major metabolites in the urine. Dopamine may also be converted to noradrenaline, in which case the major metabolites are vanillylmandelic acid

and dihydroxymandelic acid.

Carbidopa: In the absence of biogenic amine precursors, carbidopa is singularly inert pharmacologically. Carbidopa lacks effects upon blood pressure in normal, neurogenic hypertensive, or renal hypertensive dogs. It also does not affect heart rate, exhibit ganglionic, adrenergic, or peripheral anticholinergic properties, or influence renal electrolyte excretion in this species. In mice or rats, carbidopa does not appreciably affect gastric secretion, nor gastric or colonic motility. The compound does not antagonize electroshock or pentylenetetrazol - induced convulsions in mice; neither does it exhibit analgesic activity or affect fixed interval-fixed ratio reinforcement behaviour in rats. Overt behavioural effects have not been observed with carbidopa in the rhesus monkey, dog, rat, mouse or pigeon. The dose levels of carbidopa used in the latter investigations were in excess of those necessary to inhibit aromatic amino acid decarboxylase or to alter the actions of levodopa. The studies suggest that carbidopa, when administered alone at dose levels effective in inhibiting aromatic amino acid decarboxylases, lacks appreciable effects upon the cardiovascular, gastrointestinal, renal or central nervous systems.

Levodopa and Carbidopa Combination: Decarboxylation within peripheral organs and the walls of the brain capillaries limits the portion of an administered dose of levodopa accessible to most central nervous structures. Inhibition of peripheral aromatic amino acid decarboxylase enhances the accumulation of levodopa in the blood and increases the amount of this amino acid available to the brain. If brain decarboxylase is not also inhibited, the result is a marked accumulation of dopamine in the brain. Such a mechanism explains the marked enhancement of brain dopa and dopamine levels which results when levodopa is administered in combination with carbidopa which does not penetrate central nervous system structures even when administered in high doses. Levodopa increases motor activity and irritability and antagonizes reserpine-induced hypothermia, suppressed locomotion, and ptosis in mice. All these effects are enhanced two-to-six-fold by pre-treatment with carbidopa. Increased motor activity induced by levodopa in rats also is enhanced by pre-treatment with carbidopa. In contrast, levodopa-induced vomiting is decreased significantly in dogs and pigeons by pre-treatment with carbidopa.

Metabolism: Carbidopa is incompletely absorbed in the rat, dog and rhesus monkey. Following oral administration of a dose of ^{14}C labelled drug, the percentages of radioactive carbon excreted in urine and feces were:

	URINE	**FECES**
RAT	**16**	**52**
DOG	**66**	**11**
MONKEY	**40**	**32**

Urines contained both unchanged drug and metabolites.

Tissue distribution of radioactivity in rats, sacrificed one hour after an intravenous dose of 20-mg/kg of ^{14}C-carbidopa, showed the major portion of radioactivity to be concentrated in the kidneys, lungs, small intestine, and liver; in descending order. None was detected in the brain. Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinson's disease, maximal plasma levels of radioactivity were reached in two to four hours in the healthy subjects and in one and one-half to five hours in the patients. Approximately equal quantities were excreted in the urine and the feces by both groups. Comparison of urinary metabolites in healthy subjects and patients indicated that the drug is metabolized to the same degree in both. Urinary excretion of unchanged drug was essentially complete in seven hours and represented 35% of the total urinary radioactivity. Only metabolites were present thereafter. In monkeys, an oral dose of levodopa given one hour after a dose of radioactive labelled carbidopa had no significant effect on the absorption or excretion of carbidopa. Peak plasma levels of radioactivity were achieved in the same period of time and disappeared at the same rate as with carbidopa alone.

17 SUPPORTING PRODUCT MONOGRAPHS

1. SINEMET® (Levodopa and Carbidopa Tablets; 100 mg / 25 mg, and 250 mg / 25 mg), submission control 246915, Product Monograph, Organon Canada Inc., April 22, 2021.

2. APO-LEVOCARB (Levodopa and Carbidopa Tablets, USP; 100 mg / 10 mg, 100 mg / 25 mg, 250 mg / 25 mg), Control Number: 255612, Product Monograph, APOTEX INC., January 18, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr**AG-Levocarb**
Levodopa and Carbidopa Tablets, USP

Read this carefully before you start taking **AG-Levocarb** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AG-Levocarb**.

Serious Warnings and Precautions

You can suddenly fall asleep without any warning while taking AG-Levocarb. You should not:

- drive
- use machines or
- take part in activities that require you to be alert.

You may put yourself and others at risk for serious injury or death. If this happens to you, contact your doctor **right away**.

Falling asleep suddenly without warning has also been reported in patients taking other similar drugs to treat Parkinson's disease.

What is AG-Levocarb used for?
AG-Levocarb is used to treat the symptoms of Parkinson's disease in adults.

How does AG-Levocarb work?
AG-Levocarb contains two ingredients:

- Levodopa: this acts to replenish dopamine in the brain
- Carbidopa: ensures that enough levodopa gets to the brain where it is needed.

It is believed that the symptoms of Parkinson's disease are caused by a lack of dopamine. Dopamine is a naturally occurring chemical produced by certain brain cells. It has the role of relaying messages in certain regions of the brain that control muscle movement. Difficulty in movement results when too little dopamine is produced.

In many patients, this reduces the symptoms of Parkinson's disease.

What are the ingredients in AG-Levocarb?
Medicinal ingredients: Levodopa and Carbidopa

Non-medicinal ingredients: Crospovidone, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

AG-Levocarb 100 mg / 10 mg and 250 mg / 25 mg tablets also contain Indigotine AL Lake and Brilliant blue FCF lake.

AG-Levocarb 100 mg / 25 mg tablets contain D&C Yellow No. 10 lake.

AG-Levocarb comes in the following dosage forms:
Tablets: 100 mg / 25 mg (yellow), 100 mg / 10 mg and 250 mg / 25 mg (blue).

AG-Levocarb tablets are available in a levodopa:carbidopa 4:1 ratio (Levodopa and Carbidopa Tablets 100 mg / 25 mg) and in a 10:1 ratio of levodopa to carbidopa (Levodopa and Carbidopa Tablets 100 mg / 10 mg and 250 mg / 25 mg).

Do not use AG-Levocarb if:

- you are allergic to any of its ingredients.
- you are taking certain monoamine oxidase (MAO) inhibitor medicines (such as those used for depression). You must stop using MAO inhibitor medicines at least two weeks before starting therapy with AG-Levocarb.
- you have untreated heart, liver, kidney, lung, blood or hormonal disease.
- you have narrow-angle glaucoma
- you have been told that you should not take sympathomimetic medicines such as:
    - isoproterenol
    - amphetamines
    - epinephrine
- you have any suspicious skin lesions (moles) which have not been examined by your doctor or if you have ever had skin cancer.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AG-Levocarb. Talk about any health conditions or problems you may have, including if you:

- are taking or have taken levodopa in the past
- have a history of heart problems (hear attack and arrhythmias). Your doctor should carefully monitor you in an appropriate facility when you first start taking AG-Levocarb.
- have or have had ulcers in your gut (called "duodenal" or "peptic ulcer")
- have a history of convulsions/seizures
- have severe uncontrolled involuntary movements that can look like fidgeting, writhing or swaying called dyskinesia
- have any unusual conditions related to your eyes or eyesight (glaucoma)
- are going to have an operation that requires general anesthesia
- suffer from a medical condition called psychosis

- have or had skin cancer (melanoma)
- are pregnant, think you may be pregnant or become pregnant while taking AG-Levocarb. Your doctor will advise whether you should take AG-Levocarb while you are pregnant.
- are breastfeeding or wish to breastfeed. Your doctor will decide whether you should take AG-Levocarb while breastfeeding.
- have allergies
- have problems with your lungs
- have problems with your kidneys
- have problems with your liver
- have hormonal problems

Other warnings you should know about:

Laboratory tests and monitoring: When you take AG-Levocarb for a prolonged time, your doctor may:

- monitor your liver, kidney and heart function
- do blood tests

Physical activity: As you improve on AG-Levocarb you may increase your physical activity slowly depending if you have any other medical conditions.

Uncontrollable movements: AG-Levocarb may cause uncontrollable movements and "on and off" episodes. This may happen soon after you take AG-Levocarb.

Mental health changes/disturbances: AG-Levocarb may cause changes to your mental health.

- Tell you doctor **right away** if you start to feel depressed or have thoughts of suicide.
- Hallucinations (seeing or hearing things that are not there) can occur when taking AG-Levocarb.

Neuroleptic malignant syndrome: This is a disorder that causes you to have a high fever, confusion, altered states or consciousness and stiffness in your muscles. Neuroleptic malignant syndrome may happen if you suddenly:

- Reduce your dose
- Stop taking AG-Levocarb
- Switch medicines

Your doctor should monitor you when your dose is reduced or when you stop taking AG-Levocarb, especially if you take neuroleptics.

Driving and operating machinery: AG-Levocarb may cause you to feel sleepy or to fall asleep without warning. You should not drive or operate machinery until you know how AG-Levocarb

affects you. If you ever feel sleepy or fall asleep without warning, do not drive or operate machinery, and tell your doctor **right away**.

Compulsive behaviours: While taking AG-Levocarb, you may have unusual urges and/or behaviours such as excessive:

- gambling
- sexual behaviour
- eating
- spending

You or your caregiver should tell your doctor if either of you notice that you have new or changes to your behaviour.

Skin: People with Parkinson's disease have a higher risk of developing skin cancer (melanoma). Your doctor should monitor you for skin cancer while you are taking AG-Levocarb. Tell your doctor if you have:

- suspicious, undiagnosed changed patches of pigmented skin
- irritated or irregular moles
- moles in which you have noticed changes

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AG-Levocarb:

- antihypertensive drugs (used to treat elevated blood pressure)
- some medications used to treat psychiatric conditions or mental depression (including phenothiazines, butyrophenones, risperidone, selegiline, tricyclic antidepressants and MAO inhibitors)
- phenytoin (anti-epileptic medication)
- papaverine (medication for intestinal spasms)
- tetrabenazine (medication used to treat conditions related to involuntary movements such as Huntingtons Disease)
- isoniazid (medication to treat tuberculosis)
- anesthetics (drugs used during surgery)
- iron salts (such as multivitamins tablets)
- metoclopramide (for nausea and vomiting)
- Foods that are high in protein. This includes meat, fish, dairy products, seeds and nuts

How to take AG-Levocarb:

Usual dose:
Your doctor will tell you exactly how many tablets of AG-Levocarb you will need take each day

and when you should take them. AG-Levocarb tablets have a score-line on one side. Breaking the tablet in half may not give you half the dose.

DO NOT:

- stop taking AG-Levocarb, reduce the amount of AG-Levocarb you take or change your dose unless your doctor tells you to. If you suddenly stop or reduce your dose, you may experience the following symptoms: stiff muscles, fever and mental changes
- take any other antiparkinson medicines without first consulting your doctor. This includes other medicines containing levodopa and carbidopa
- give AG-Levocarb to other people
- use AG-Levocarb for any other condition

Tell your doctor **right away** if you notice any changes in your symptoms, such as nausea or abnormal movements. Your doctor may need to adjust your dose.

Overdose:

If you think you, or a person you are caring for, have taken too much AG-Levocarb, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a dose, take it as soon as you remember. If it is almost time to take your next dose, do not take the dose you have missed, and take your next dose as scheduled.

What are possible side effects from using AG-Levocarb?
These are not all the possible side effects you may have when taking AG-Levocarb. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- Nausea
- Vomiting
- Slow movements
- Sleepiness
- Dizziness
- Mental changes
- Dream abnormalities
- Hair loss
- Dark-coloured saliva, urine and sweat
- Eating disorder (anorexia)

- Chest pain
- Feeling weak and tired
- High blood pressure
- Low blood pressure
- Stomach pain
- Dry mouth
- Changes in tastes
- Diarrhea
- Constipation
- Back and shoulder pain
- Muscle cramps
- Bladder infection
- Drooling
- Burning sensation of the tongue
- Hiccups
- Gas
- Heart burn
- Grinding or clenching of teeth
- Weight loss
- Weight gain
- Leg pain
- Blurred vision
- Double vision
- Spasms that move the eye(s) into a fixed position (oculogyric crisis)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Dyskinesia: severe uncontrolled movements		√	
COMMON			
Hallucinations: seeing or hearing things that are not there		√	
RARE			
Allergic reactions: hives, itching, rash, swelling of the face, lips, mouth, tongue or throat, trouble breathing and/or swallowing			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Compulsive Behaviour: Inability to resist the impulse to perform an action that could be harmful such as gambling too much, increased sexual urges, uncontrollable urge to eat or spend money, or repeating meaningless actions		√	
Convulsion: seizure, spasms, shaking or fits		√	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		√	
Excessive sleepiness or falling asleep without warning while doing normal activities		√	
Feeling of lightheaded-ness as when standing quickly		√	
Melanoma (skin cancer): Changed patches of pigmented skin, including irritated or irregular moles, or moles in which you have noticed changes		√	
Neuroleptic Malignant Syndrome: pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness		√	
Priapism: Long-lasting (greater than 4 hours in duration) and painful erection of the penis		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Uneven (irregular) heartbeat, palpitations, chest pain and/or discomfort, pain in jaw, shoulders, arm and/or back, shortness of breath, sweating, nausea or light-headedness		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature, 15-30°C, in a tightly closed container.
Protect from light and moisture.
Keep out of reach and sight of children.
Do not use outdated medicine.

If you want more information about AG-Levocarb:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-450-449-9272.

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