

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214869Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DHIVY safely and effectively. See full prescribing information for DHIVY.

**DHIVY (carbidopa and levodopa) tablets, for oral use**  
**Initial U.S. Approval: 1975**

### INDICATIONS AND USAGE

DHIVY is a combination of carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid) indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. (1)

### DOSAGE AND ADMINISTRATION

- The recommended starting dosage of DHIVY is one 25 mg /100 mg tablet taken orally three times a day. (2.1)
- Dosage may be increased by up to one whole tablet every day or every other day, as needed, until a maximum dosage of eight whole tablets of DHIVY a day is reached. (2.1)
- Swallow DHIVY with or without food. (2.3)

### DOSAGE FORMS AND STRENGTHS

Tablets: Carbidopa and levodopa 25 mg/100 mg, functionally scored. Each DHIVY tablet has 3 functional scores with each segment containing 6.25 mg of carbidopa and 25 mg of levodopa. (3)

### CONTRAINDICATIONS

- Nonselective MAO inhibitors (4)
- With known hypersensitivity to any component of DHIVY (4)

### WARNINGS AND PRECAUTIONS

- May cause falling asleep during activities of daily living. (5.1)
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion. (5.2)
- Cardiovascular Ischemic Events: Monitor patients with a history of cardiovascular disease. (5.3)
- Hallucinations/Psychosis may occur. (5.4)
- Impulse Control/Compulsive Behaviors: Consider dose reduction or stopping DHIVY if impulse control disorders occur. (5.5)
- May cause or exacerbate dyskinesia: Consider dose reduction. (5.6)

### ADVERSE REACTIONS

The most common adverse reactions reported with carbidopa/levodopa tablets have included dyskinesias, such as choreiform, dystonic, and other involuntary movements, and nausea. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Riverside Pharmaceuticals at 1-800-612-8466 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

Iron salts and dopamine D2 antagonists including metoclopramide: May reduce the effectiveness of DHIVY. (7.2, 7.3)

### USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

Revised: 11/2021

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Initial Dosage and Maintenance of Therapy
- 2.2 Discontinuation of DHIVY
- 2.3 Administration Information

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Falling Asleep During Activities of Daily Living and Somnolence
- 5.2 Withdrawal-Emergent Hyperpyrexia and Confusion
- 5.3 Cardiovascular Ischemic Events
- 5.4 Hallucinations/Psychotic-Like Behavior
- 5.5 Impulse Control/Compulsive Behaviors
- 5.6 Dyskinesia
- 5.7 Peptic Ulcer Disease
- 5.8 Glaucoma
- 5.9 Laboratory Tests
- 5.10 Depression/Suicidality

### 6 ADVERSE REACTIONS

### 7 DRUG INTERACTIONS

- 7.1 Monoamine Oxidase (MAO) Inhibitors
- 7.2 Dopamine D<sub>2</sub> Receptor Antagonists and Isoniazid
- 7.3 Iron Salts

### 7.4 Antihypertensive Drugs

### 7.5 Dopamine-Depleting Agents

### 7.6 Metoclopramide

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

#### 8.2 Lactation

#### 8.4 Pediatric Use

#### 8.5 Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

#### 12.2 Pharmacodynamics

#### 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

#### 16.2 Storage and Handling

### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

DHIVY is indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Initial Dosage and Maintenance of Therapy**

The recommended starting dosage of DHIVY is one 25 mg / 100 mg tablet taken orally three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by up to one whole tablet every day or every other day, as needed to a maximum daily dosage of eight whole tablets.

Dosing with DHIVY should be individualized and adjusted according to clinical response and tolerability. The tablet is functionally scored to facilitate dose adjustment. At least 70 mg to 100 mg of carbidopa per day should be provided. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Monitor patients closely during the dose adjustment period. Specifically, involuntary movements may occur with DHIVY, which may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Maintain patients on the lowest dosage required to achieve symptomatic control and to minimize adverse reactions, such as dyskinesia and nausea.

#### **2.2 Discontinuation of DHIVY**

Avoid sudden discontinuation or rapid dose reduction of DHIVY. The daily dosage of DHIVY should be tapered at the time of treatment discontinuation [*see Warnings and Precautions (5.2)*].

If general anesthesia is required, DHIVY may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling neuroleptic malignant syndrome, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

#### **2.3 Administration Information**

Swallow DHIVY with or without food. The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa.

If the patient has difficulty swallowing the tablet due to its size, the tablet can be broken at the score lines.

### **3 DOSAGE FORMS AND STRENGTHS**

DHIVY tablets are white to off-white tablets containing 25 mg of carbidopa and 100 mg of levodopa. Each DHIVY tablet has 3 functional scores with each segment containing 6.25 mg of carbidopa and 25 mg of levodopa.

### **4 CONTRAINDICATIONS**

DHIVY is contraindicated in patients

- Currently taking a nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, linezolid, and tranylcypromine) or have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently [*see Drug Interactions (7.1)*].
- With known hypersensitivity to any component of DHIVY [*see Adverse Reactions (6)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Falling Asleep During Activities of Daily Living and Somnolence**

Patients taking carbidopa/levodopa alone or with other dopaminergic drugs have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities of daily living, including the operation of motor vehicles which have resulted in accidents. Although many patients reported somnolence while on dopaminergic medications, some perceived that they had no warning signs (sleep attack), such as excessive drowsiness, and believed that they were alert immediately prior to the event. Sudden onset of sleep has been reported to occur more than one year after the initiation of treatment.

It has been reported that falling asleep while engaged in activities of daily living usually occurs in a setting of pre-existing somnolence, although some patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness in DHIVY-treated patients, especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with DHIVY, advise patients about the potential to develop drowsiness and ask specifically about factors that may increase the risk for somnolence with DHIVY such as the use of concomitant sedating medications and the presence of sleep disorders. Consider discontinuing DHIVY in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.). If treatment with DHIVY continues, advise patients not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There

is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

## **5.2 Withdrawal-Emergent Hyperpyrexia and Confusion**

A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy. Avoid sudden discontinuation or rapid dose reduction in patients taking DHIVY. If the decision is made to discontinue DHIVY, the dose should be tapered to reduce the risk of hyperpyrexia and confusion [*see Dosage and Administration (2.2)*].

## **5.3 Cardiovascular Ischemic Events**

In patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias, cardiac function should be monitored in an intensive cardiac care facility during the period of initial dosage adjustment.

## **5.4 Hallucinations/Psychotic-Like Behavior**

Hallucinations and psychotic-like behavior have been reported with dopaminergic medications. In general, hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion, sleep disorder (insomnia), and excessive dreaming.

Abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should not be treated with DHIVY, because of the risk of exacerbating psychosis. In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of DHIVY [*see Drug Interactions (7.2)*].

## **5.5 Impulse Control/Compulsive Behaviors**

Case reports suggest that patients can experience an intense urge to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including DHIVY, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dosage was reduced or the medication was discontinued.

Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or the caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with DHIVY.

Consider dosage reduction or stopping the medication if a patient develops such urges while taking DHIVY.

### **5.6 Dyskinesia**

DHIVY can cause dyskinesias that may require a dosage reduction of DHIVY or other medications used for the treatment of Parkinson's disease.

### **5.7 Peptic Ulcer Disease**

Treatment with DHIVY may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

### **5.8 Glaucoma**

DHIVY may cause increased intraocular pressure in patients with glaucoma. Monitor intraocular pressure in patients with glaucoma after starting DHIVY.

### **5.9 Laboratory Tests**

DHIVY may cause a positive Coombs test or false-positive reaction for urinary ketone bodies when a test tape 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 on carbidopa-levodopa therapy have been reported. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on carbidopa levodopa therapy.

### **5.10 Depression/Suicidality**

All patients taking DHIVY should be observed carefully for the development of depression with concomitant suicidal tendencies.

## **6 ADVERSE REACTIONS**

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Falling Asleep During Activities of Daily Living and Somnolence [*see Warnings and Precautions (5.1)*]
- Withdrawal-Emergent Hyperpyrexia and Confusion [*see Warnings and Precautions (5.2)*]
- Cardiovascular Ischemic Events [*see Warnings and Precautions (5.3)*]
- Hallucinations/Psychotic-Like Behavior [*see Warnings and Precautions (5.4)*]
- Impulse Control/Compulsive Behaviors [*see Warnings and Precautions (5.5)*]
- Dyskinesia [*see Warnings and Precautions (5.6)*]
- Peptic Ulcer Disease [*see Warnings and Precautions (5.7)*]

- Glaucoma [*see Warnings and Precautions (5.8)*]
- Depression//Suicidality [*see Warnings and Precautions (5.10)*]

The most common adverse reactions reported with carbidopa/levodopa tablets have included dyskinesias, such as choreiform, dystonic, and other involuntary movements, and nausea.

The following other adverse reactions have been reported with carbidopa/levodopa tablets:

*Body as a Whole*

Chest pain, asthenia.

*Cardiovascular*

Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

*Gastrointestinal*

Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

*Hematologic*

Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

*Hypersensitivity*

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

*Musculoskeletal*

Back pain, shoulder pain, muscle cramps.

*Nervous System/Psychiatric*

Psychotic episodes including delusions, hallucinations, and paranoid ideation, bradykinetic episodes (“on-off” phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with DHIVY has not been established.

*Respiratory*

Dyspnea, upper respiratory infection.

*Skin*

Rash, increased sweating, alopecia, dark sweat.

*Urogenital*

Urinary tract infection, urinary frequency, dark urine.

### *Laboratory Tests*

Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), LDH, bilirubin, BUN, Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

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

### *Body as a Whole*

Abdominal pain and distress, fatigue.

### *Cardiovascular*

Myocardial infarction.

### *Gastrointestinal*

Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

### *Metabolic*

Edema, weight gain, weight loss.

### *Musculoskeletal*

Leg pain.

### *Nervous System/Psychiatric*

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

### *Respiratory*

Pharyngeal pain, cough.

### *Skin*

Malignant melanoma, flushing.

### *Special Senses*

Oculogyric crises, diplopia, blurred vision, dilated pupils.

### *Urogenital*

Urinary retention, urinary incontinence, priapism.

### *Miscellaneous*

Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.



## **7 DRUG INTERACTIONS**

### **7.1 Monoamine Oxidase (MAO) Inhibitors**

The use of nonselective MAO inhibitors with DHIVY is contraindicated [*see Contraindications (4)*]. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating DHIVY.

DHIVY may be administered concomitantly with the manufacturer's recommended dose of selective MAO-B inhibitors (e.g., rasagiline or selegiline HCl). Concomitant therapy with selegiline and carbidopa/levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa/levodopa alone.

### **7.2 Dopamine D<sub>2</sub> Receptor Antagonists and Isoniazid**

Dopamine D<sub>2</sub> receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the effectiveness of levodopa. Monitor patients taking these drugs with DHIVY for worsening Parkinson's symptoms.

### **7.3 Iron Salts**

Iron salts or multivitamins containing iron salts can form chelates with levodopa and carbidopa and can cause a reduction in the bioavailability of DHIVY. If iron salts or multivitamins containing iron salts are co-administered with DHIVY, monitor patients for worsening Parkinson's symptoms.

### **7.4 Antihypertensive Drugs**

Symptomatic postural hypotension occurred when carbidopa/levodopa was added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with DHIVY is started, dosage adjustment of the antihypertensive drug may be required.

### **7.5 Dopamine-Depleting Agents**

Use of DHIVY with dopamine-depleting agents (e.g., reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

### **7.6 Metoclopramide**

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also reduce effectiveness of levodopa by its dopamine receptor antagonistic properties.

## **8 USE IN SPECIFIC POPULATIONS**

## 8.1 Pregnancy

### Risk Summary

There are no adequate data on the developmental risk associated with the use of DHIVY in pregnant women. In animal studies, carbidopa/levodopa has been shown to be developmentally toxic (including teratogenic effects) at clinically relevant doses (*see Data*).

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### Data

#### *Animal Data*

When administered to pregnant rabbits throughout organogenesis, carbidopa-levodopa caused both visceral and skeletal malformations in fetuses at all doses and ratios of carbidopa-levodopa tested. No teratogenic effects were observed when carbidopa-levodopa was administered to pregnant mice throughout organogenesis.

## 8.2 Lactation

### Risk Summary

Levodopa has been detected in human milk after administration of carbidopa-levodopa. There are no data on the presence of carbidopa in human milk, the effects of levodopa or carbidopa on the breastfed infant, or the effects on milk production. However, inhibition of lactation may occur because levodopa decreases secretion of prolactin in humans.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DHIVY and any potential adverse effects on the breastfed infant from DHIVY or from the underlying maternal condition.

## 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

## 8.5 Geriatric Use

Of the total number of subjects in clinical studies of immediate-release carbidopa-levodopa tablets (i.e., Sinemet<sup>®</sup>), almost half of the patients were older than age 65 years, and few were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals to adverse drug reactions such as hallucinations cannot be ruled out.

The systemic exposure of levodopa was increased in elderly subjects compared to young subjects [see *Clinical Pharmacology (12.3)*]. There is no specific dosing recommendation based upon clinical pharmacology data as carbidopa/levodopa is titrated as tolerated for clinical effect.

## 10 OVERDOSAGE

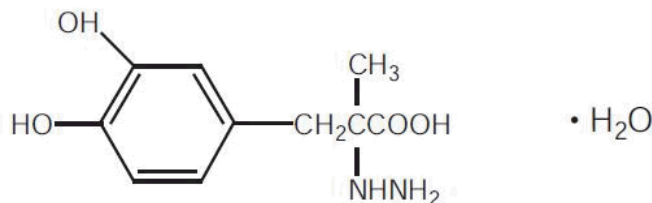
Based on the limited available information, the acute symptoms of levodopa/dopa decarboxylase inhibitor overdose can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g., hypotension, tachycardia) and more severe psychiatric problems at higher doses. An isolated report of rhabdomyolysis and another of transient renal insufficiency suggest that levodopa overdose may give rise to systemic complications, secondary to dopaminergic overstimulation.

Monitor patients and provide supportive care. Patients should receive electrocardiographic monitoring for the development of arrhythmias; if needed, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration.

## 11 DESCRIPTION

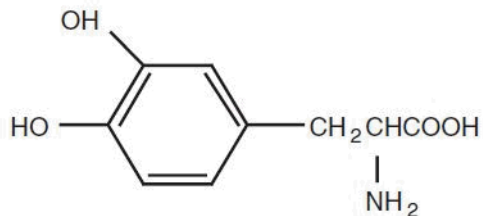
DHIVY<sup>®</sup> (carbidopa levodopa) is a combination of carbidopa, an inhibitor of aromatic amino acid decarboxylation, and levodopa, an aromatic amino acid, in tablets for oral use.

Carbidopa is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (–)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxy-benzene) propanoic acid monohydrate. It has a pKa of 2.3. Its molecular formula is C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>•H<sub>2</sub>O and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (–)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. It has a pKa of 2.32. Its molecular formula is C<sub>9</sub>H<sub>11</sub>NO<sub>4</sub> and its structural formula is:



DHIVY is supplied as tablets for oral administration containing 25 mg of carbidopa and 100 mg of levodopa. The inactive ingredients are magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Carbidopa

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain.

#### Levodopa

Levodopa is the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa treats symptoms of Parkinson's disease.

### 12.2 Pharmacodynamics

Because its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available to the brain. Carbidopa does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, 'on-off' phenomenon, and akinesia.

### 12.3 Pharmacokinetics

Following single oral administration of a DHIVY tablet, DHIVY was shown to be bioequivalent to an immediate-release carbidopa/levodopa 25/100 mg tablet under fasting conditions for both carbidopa and levodopa.

## Absorption

Following oral dosing of DHIVY under fasted conditions, the maximum concentration occurred at 3 hours for carbidopa and 1 hour for levodopa. The exposure of DHIVY after dose fractionation is proportional.

### *Effect of Food*

In healthy adults, oral administration of DHIVY after a high-fat, high-calorie meal reduced levodopa  $C_{max}$  by approximately 25% while the AUC remained unchanged. The peak concentration of both carbidopa/levodopa were observed approximately 30 minutes later when DHIVY is taken with a high-fat, high-calorie meal.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet [*see Dosage and Administration (2.3)*].

## Distribution

Carbidopa is approximately 36% bound to plasma proteins. Levodopa is approximately 10% to 30% bound to plasma proteins.

## Elimination

Following oral dosing of DHIVY under fasted conditions, the half-life was reported at approximately 3.5 hours for carbidopa and 2 hours for levodopa.

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.

## Specific Populations

### *Geriatric Patients*

A study in eight young healthy subjects (21-22 years) and eight elderly healthy subjects (69-76 years) showed that the absolute bioavailability of levodopa was similar between young and elderly subjects following oral administration of levodopa and carbidopa. However, the systemic exposure (AUC) of levodopa was increased by 55% in elderly subjects compared to young subjects. Based on another study in forty patients with Parkinson's disease, there was a correlation between age of patients and the increase of AUC of levodopa following administration of levodopa and an inhibitor of peripheral dopa decarboxylase. AUC of levodopa was increased by 28% in elderly patients ( $\geq 65$  years) compared to young patients ( $< 65$  years). Additionally, mean value of  $C_{max}$  for levodopa was increased by 24% in elderly patients ( $\geq 65$  years) compared to young patients ( $< 65$  years) [*see Use in Specific Populations (8.5)*].

The AUC of carbidopa was increased in elderly subjects (n=10, 65-76 years) by 29% compared to young subjects (n=24, 23-64 years) following IV administration of 50 mg levodopa with carbidopa (50 mg). This increase is not considered to have a clinically significant impact.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

In rats, oral administration of carbidopa-levodopa for two years resulted in no evidence of carcinogenicity.

#### Impairment of Fertility

In reproduction studies, no effects on fertility were observed in rats receiving carbidopa-levodopa.

## **14 CLINICAL STUDIES**

The efficacy of DHIVY is based upon bioavailability studies comparing DHIVY to an immediate-release tablet containing 25 mg of carbidopa and 100 mg of levodopa [*see Clinical Pharmacology (12.3)*].

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

DHIVY (carbidopa and levodopa) tablets are white to off-white tablets with functional scoring containing 25 mg of carbidopa and 100 mg of levodopa. One side of each DHIVY tablet has 3 scores, with each segment containing 6.25 mg of carbidopa and 25 mg of levodopa (1:4 ratio). The unscored side of the tablet is debossed with logo "AV701".

DHIVY is supplied as follows:

NDC 77334-701-01 bottles of 100.

### **16.2 Storage and Handling**

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]. Store in a tightly closed container, protected from light and moisture.

Dispense in a light-resistant container.

## 17 PATIENT COUNSELING INFORMATION

### Dosing Instructions

- It is important that DHIVY be taken at regular intervals according to the schedule outlined by their physician. Inform the patient not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting their physician. Advise patients to call their healthcare provider before stopping DHIVY. Discontinue DHIVY slowly. Tell patients to call their healthcare provider if they develop withdrawal symptoms such as fever and confusion [*see Dosage and Administration (2.2) and Warnings and Precautions (5.2)*].
- Advise patients to swallow DHIVY with or without food. If the patient has difficulty swallowing the tablet due to its size, inform the patient that the tablet can be broken at the score lines [*see Dosage and Administration (2.3)*].
- Advise the patient that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of DHIVY. Although the color appears to be clinically insignificant, garments may become discolored.
- Advise the patient that a change in diet to foods that are high in protein or taking iron salts or multivitamins with iron may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa.

### Falling Asleep

Advise patients that certain side effects such as sleepiness and dizziness that have been reported with DHIVY may affect some patients' ability to drive and operate machinery safely [*see Warnings and Precautions (5.1) and Adverse Reactions (6)*].

### Hallucinations and Psychosis

Inform patients that hallucinations can occur with levodopa products [*see Warnings and Precautions (5.4)*].

### Impulse Control Disorder

Inform patients of the potential for experiencing intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease [*see Warnings and Precautions (5.5)*].

### Dyskinesia

Instruct patients to notify their healthcare provider if abnormal involuntary movements appear or get worse during treatment with DHIVY [*see Warnings and Precautions (5.6)*].

### Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during DHIVY therapy [*see Use in Specific Populations (8.1)*].

Advise female patients to notify their physicians if they intend to breastfeed or are breastfeeding an infant [*see Use in Specific Populations (8.2)*].

Distributed by:  
Riverside Pharmaceuticals Corporation  
Washington, DC 20006, USA

U.S. Patent 11,033,521



-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

TERESA J BURACCHIO  
11/12/2021 12:27:42 PM