

**National PBM Abbreviated Drug Monograph**  
**Carbidopa/Levodopa/Entacapone (Stalevo®)**

June 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

**Executive Summary:**

- Stalevo® can provide the benefits of levodopa/carbidopa plus entacapone with greater convenience by allowing the administration of fewer pills per day.
- Pharmacokinetic studies have demonstrated bioequivalence between Stalevo® and levodopa/carbidopa IR plus entacapone.
- Switching from levodopa/carbidopa IR alone to the corresponding dose Stalevo® tablet is analogous to adding entacapone.

**Introduction**

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating the combination product Stalevo® for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

**Pharmacology/Pharmacokinetics<sup>1</sup>**

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When entacapone is given in conjunction with levodopa and an aromatic amino decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. Also, the higher levodopa levels lead to increased levodopa adverse effects, at times requiring a decrease in the dose of levodopa. Entacapone lacks activity on parkinsonian symptoms when given alone. Because of their similar pharmacokinetic profiles, entacapone and levodopa/carbidopa are routinely administered together in clinical practice. A combination product should provide the same pharmacokinetic profile and clinical effects as levodopa/carbidopa plus entacapone taken together, while affording greater convenience.

**FDA Approved Indication(s) and Off-label Uses<sup>1</sup>**

The levodopa/carbidopa/entacapone formulation is approved (1) to substitute (with equivalent strength of each of the 3 components) for immediate-release (IR) levodopa/carbidopa plus entacapone, which were previously administered as individual products; or, (2) to replace levodopa/carbidopa IR (without entacapone) when patients

experience the signs and symptoms of end-of-dose "wearing off." This second indication is for patients who are taking a total daily dose of levodopa of 600 mg or less and are not experiencing dyskinesias. Switching to levodopa/carbidopa/entacapone (with an equivalent levodopa dose) from levodopa/carbidopa IR alone is analogous to adding entacapone. Patients with a history of dyskinesia or those who are taking more than 600 mg of levodopa per day are more likely to require a reduction in daily levodopa dose when entacapone is added.

### **Current VA National Formulary Alternatives**

Currently, the VANF contains carbidopa/levodopa in both immediate and sustained release preparations and entacapone tablets.

### **Dosage and Administration**<sup>1,2</sup>

The recommended dose of entacapone is a 200 mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times per day. Clinical experience with doses over 1600 mg is limited.

There is no experience in transferring patients currently treated with formulation of carbidopa/levodopa other than immediate release carbidopa/levodopa with a 1:4 ratio (controlled release formulations, or standard release presentations with a 1:10 ratio of carbidopa/levodopa) and entacapone to the carbidopa, levodopa, and entacapone combination tablet.

Patients who are currently treated with an entacapone 200 mg tablet with each dose of standard release levodopa/carbidopa can be directly switched to the corresponding strength of carbidopa, levodopa, and entacapone combination containing the same amounts of levodopa and carbidopa. For example, patients receiving 1 tablet of standard release carbidopa/levodopa 25/100 mg and 1 tablet of entacapone 200 mg at each administration can be switched to a single Stalevo 100 tablet (containing 25 mg of carbidopa, 100 mg of levodopa, and 200 mg of entacapone).

In patients with Parkinson disease who experience the signs and symptoms of end-of-dose "wearing-off" on their current standard release carbidopa/levodopa treatment, clinical experience shows that patients with a history of moderate or severe dyskinesias or taking more than 600 mg/day of levodopa are likely to require a reduction in daily levodopa dose when entacapone is added to their treatment. Since dose adjustment of the individual components is impossible with fixed dose products, it is recommended that patients first be titrated individually with a carbidopa/levodopa product (ratio 1:4) and an entacapone product, and then transferred to a corresponding dose of carbidopa, levodopa, and entacapone combination once the patient's status has stabilized.

In patients who take a total daily levodopa dose up to 600 mg and who do not have dyskinesias, an attempt can be made to transfer to the corresponding daily dose of carbidopa, levodopa, and entacapone combination. However, even in these patients, a

reduction of carbidopa/levodopa or entacapone may be necessary, and the provider is reminded that this may not be possible with carbidopa, levodopa, and entacapone combination. Because entacapone prolongs and enhances the effects of levodopa, individualize therapy and adjust if necessary according to the desired therapeutic response.

It is also possible to switch patients receiving levodopa/carbidopa controlled-release (CR) plus entacapone to the levodopa/carbidopa/entacapone formulation. The bioavailability of levodopa from levodopa/carbidopa CR is approximately 70% to 75% of levodopa/carbidopa IR.<sup>3</sup> Therefore, the levodopa AUC (concentration area under the curve) produced by levodopa/carbidopa CR 200 mg/50 mg plus entacapone 200 mg should be approximately comparable to levodopa/carbidopa/entacapone 150. However, levodopa from the levodopa/carbidopa/entacapone formulation has a  $t_{max}$  similar to that of levodopa/carbidopa IR (0.5-1.5 hours), whereas absorption is more delayed from levodopa/carbidopa CR ( $t_{max}$  = 1.5-3 hours).<sup>3</sup> These differences in pharmacokinetic profile need to be considered, but in general, a shorter time to onset of levodopa effect is desirable in patients with motor fluctuations.

### **Efficacy**<sup>4-6</sup>

An open label, multi center trial evaluated the conversion of 169 patients experiencing end of dose wearing off and/or mild dyskinesias.<sup>4</sup> These patients were receiving levodopa/carbidopa and were converted to the combination of levodopa/carbidopa/entacapone. Patients were evaluated with the quality of life instrument PDQ-39, Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III and investigator/patient global clinical assessments. Significant improvements in the PDQ-39 and the UPDRS were seen during combination treatment (35.7 vs 31.8 and 35.4 vs 29.8, respectively,  $p < 0.001$ ). This trial demonstrated that the addition of entacapone reduced end of dose wearing off with occasional exacerbation of dyskinesias that was usually resolved with dosage adjustments in patients treated with a combination product of levodopa/carbidopa/entacapone.

Brooks, et al. demonstrated that patients receiving the separate products of levodopa/carbidopa and entacapone could be safely converted to the combination product.<sup>5</sup> This was an open, parallel-group evaluation of 176 patients. Patients were followed for six weeks and assessed with the Clinical Impression of change and UPDRS. There was no difference in treatment response between the groups; however, 81% of the patients preferred therapy with the single tablet versus two tablet regimen. Adverse events were not different between the groups.

### **Adverse Events (Safety Data)**<sup>1</sup>

#### **Most Frequent:**

Abdominal Pain with Cramps, Abnormal Mental State, Aggressive Behavior, Cardiac Arrhythmias, Constipation, Depression, Diarrhea, Dizziness, Dyskinesia, Dysuria, Fatigue, Hallucinations, Hyperkinesia, Hypokinesia, Mood Changes, Nausea, Nervousness, Nightmares, Severe Nausea, Severe Vomiting, Tremors, Urine Discoloration

**Less Frequent:**

Anorexia, Anxiety, Back Pain, Bacterial Infection, Blepharospasm, Discoloration of Sweat, Drowsiness, Dysgeusia, Dyspepsia, Dyspnea, Eyelid Closing, Fainting, Feeling Agitated, Flatulence, Flushing, Gastritis, General Weakness, Headache Disorder, Hyperhidrosis, Insomnia, Orthostatic Hypotension, Purpura, Vomiting, Xerostomia

**Rare:**

Duodenal Ulcer, Fever, Hemolytic Anemia, Hypertension, Impaired Cognition, Pulmonary Fibrosis, Rhabdomyolysis

**Drug Interactions<sup>1</sup>**

**Drug-Drug Interactions**

Monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) are the two major enzymes systems involved in the metabolism of catecholamines. Therefore, theoretically, the combination of either entacapone with a non-selective MAO inhibitor will result in inhibition of the majority of catecholamine metabolism pathways. Therefore, the concomitant use of either a non-selective MAOI or a selective MAO-A inhibitor with a selective MAO-B inhibitor with entacapone is contraindicated. Entacapone may be used with selegiline, provided that the daily dose of selegiline does not exceed 10 mg.

**Acquisition Costs**

**Table 1: FSS pricing of levodopa/carbidopa, entacapone and levodopa/carbidopa/entacapone**

Drug	Dose	Cost/tablet (\$)
Levodopa/carbidopa	10/100 mg tablet (generic)	0.10
Levodopa/carbidopa	25/100 mg tablet (generic)	0.11
Entacapone	200 mg tablet	1.20
Levodopa/carbidopa/entacapone	12.5/50/200 mg	1.31
Levodopa/carbidopa/entacapone	25/100/200 mg	1.31

Prices as of 8/05

Therefore the cost of a dose when the individual components are used is \$1.30 (0.10 +1.20) versus the combined product \$1.31.

**Pharmacoeconomic Analysis**

A Markov model has been used to demonstrate the cost effectiveness of the combination product levodopa/carbidopa/entacapone over standard of care in Parkinson's disease patients.<sup>7</sup> In this model the costs and outcomes were projected over a 10 year period and were interpreted from a societal and payer perspective. Treatment with the combination product produced an average gain of 1.04 quality adjusted life years (QALY) per patient. This therapy also resulted in an increase in direct costs per patient over the 10 year period. The incremental cost effectiveness ratio (ICER)

was £3105 per QALY gained. The added cost of the medication is likely exceeded by savings made in other areas (increased clinic appointment, increased physical therapy or homecare nursing, etc).

## **Conclusions**

The combination of levodopa/carbidopa/entacapone has been proven to be safe and effective as a management therapy for end of dose wearing off and mild dyskinesias experience by Parkinson's disease patients. Additionally, conversion to the combination product is possible in patients receiving the components separately. A pharmacoeconomic analysis demonstrated the product to be cost effective over stand care (levodopa/carbidopa and other agents such as selegiline and dopamine agonists).

## **References:**

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**Prepared January 2006. Contact person: Kathryn Tortorice Pharm D, BCPS**

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