Carbidopa/ Levodopa Extended Release Capsules (Rytary)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Carbidopa/Levodopa Extended Release Capsules (CLERC) is a formulation that contains beads of carbidopa and levodopa that are dissolved and are absorbed at different rates. This enables the formulation to provide both initial and extended levodopa plasma concentrations after a single dose.
Indication(s) Under Review in this document	Indicated for the treatment of Parkinson's disease (PD), post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Dosage Form(s) Under Review	Extended-release capsules: Carbidopa and levodopa 23.75 mg / 95 mg, 36.25 mg / 145 mg, 48.75 mg / 195 mg, 61.25 mg / 245 mg
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category C

Executive Summary	
Efficacy	• The ADVANCE-PD and ASCEND-PD trials clearly demonstrate that CLERC is more effective at reducing off time in advanced PD compared with carbidopa levodopa immediate release (CD–LD IR) and to carbidopa levodopa with entacapone (CD–LD–E). • Patients had more 'on' time while taking fewer doses, compared with CD-LD IR and CD-LD-E.
Safety	• The adverse reactions for CLERC are comparable with those for CD–LD IR. • The most common adverse events compared with placebo, included nausea, headache, dizziness and insomnia. • During the double-blind phase of the ASCEND PD trial, 20% of subjects treated with CLERC experienced adverse reactions compared with 14% of subjects treated with CD–LD–E. Six serious adverse events were recorded, including atrial fibrillation, constipation, gastroenteritis, dehydration, hyperkalemia and sciatica during CLERC treatment
Potential Impact	• In 2001 the VA created six specialized centers known as the Parkinson's Disease Research, Education, and Clinical Centers or "PADRECCs". There are 51,625 unique patients in VA diagnosed with PD. Current pharmacologic management of the disease is based on treating the symptoms of the disorder, in particular the motor symptoms. The mainstay of treatment is based on augmentation of dopamine, which is reduced in the nigrostriatal pathway and is responsible for the motor symptoms of the disorder. Development of wearing off and other motor fluctuations is a phenomenon of disease progression. As the disease

	progresses, the plasma half-life of LD becomes more critical in maintaining clinical effects and motor benefit. Doses tend to last for shorter periods as therapy progresses. The aim of CLERC is to "smooth" out these fluctuations by combining immediate and controlled release delivery of levodopa. • Patient convenience. The use of a formulation such as CLERC which is composed of both immediate release and extended release forms could lower daily pill burden for PD patients as well as decreased use of rescue medications (immediate release carbidopa/levodopa)

Background

Purpose for review

Recent FDA approval of CLERC

Issues to be determined:

✔ Evidence of need- does CLERC provide an alternative for later stages of PD
✔ Does CLERC offer advantages to currently available alternatives?
✔ Does CLERC offer advantages over current VANF agents?
✔ What safety issues need to be considered?
✔ Does CLERC have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
CARBIDOPA/LEVODOPA IR		Treatment Recommendations
CARBIDOPA/LEVODOPA SA		Treatment Recommendations

Non-formulary Alternative (if applicable)	Other Considerations	
ENTERAL SUSPENSION (Duopa)	Requires placement of J tube	
CARBIDOPA 25MG TAB		Treatment Recommendations
CARBIDOPA /ENTACAPONE /LEVODOPA TAB	Can lessen pill burden	Treatment Recommendations

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms IPX066, carbidopa/levodopa immediate release, carbidopa/levodopa sustained release and Rytary. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

A comparative pharmacokinetic study of CD-LD IR, CD-LD CR and CD-LD-E was conducted in 24 healthy volunteers.[9] The results of this study demonstrated that peak concentrations (Cmax) of LD were achieved at 1- 1.5 hours with currently available CD LD formulations, in contrast, the Cmax for CLERC occurred at 4.5 hrs. The initial increase in LD Cmax was similar between CLERC and CD-LD IR and faster than for CD-LD CR and CD-LD-E. Concentrations of LD from CLERC were sustained for approximately 5 hours and did not decrease to 10% of peak until 10.1 hours. Currently available formulations decreased to 10% of Cmax between 5-7.5 hours. Bioavailability of LD from CLERC was 83.5%, 78.3%, and 58.8% relative to CD-LD IR, CD-LD CR, and CD-LD-E, respectively. The results of this pharmacokinetic study supported the CLERC formulation demonstrating a smoother concentration time curve than currently available CD-LD preparations. Additionally, the reduced bioavailability with CD-LD CR was not seen with the CLERC formulation and use of the latter formulation should not need supplementation of CD-LD IR. The clinical benefits of this new CLERC formulation were investigated in several Phase III trials, which are described below.

The FDA approval of CLERC was based on three pivotal, randomized controlled trials. Please refer to **Table 1** for more detailed study results.

The APEX-PD trial was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose phase III study comparing with placebo in patients with early PD. This trial enrolled and randomized 381 levodopa-naive patients. The primary efficacy endpoint, a change from baseline in the sum of the United Parkinson's Disease Rating Scale (UPDRS) Parts II and III score at the end of the study was met as were several secondary endpoints. The most commonly reported adverse events in the CLERC treatment arms included nausea, headache, and dizziness, which were consistent with carbidopa/levodopa products.

The ADVANCE-PD trial was a randomized, double-blind, active-control, parallel-group phase III study of the safety and efficacy of compared with that of immediate-release carbidopa/levodopa (CD LD IR)in patients with advanced PD complicated by motor fluctuations. Before randomization, subjects receiving a stable CD LD IR regimen entered a 3-week dose-adjustment period followed by a 6-week dose-conversion period to CLERC. The trial of randomized 393 patients with advanced PD and 2-5 hours of having "off" periods daily. The study demonstrated that CLERC reduced the percentage of "off" time (36.9% to 23.8%) from baseline versus CD LD IR (36.0% to 29.8%) during waking hours to end of study. Additionally, CLERC increased "on" time without troublesome dyskinesia during waking hours versus baseline to end of study by 1.8 hours. Compared with the initially recommended CLERC regimens, 234 patients (60%) required higher doses and 61 patients (16%) required lower doses. At the end of the randomization period, dosing frequency of CLERC was 3.6 doses daily versus5.0 doses for CD LD IR. During the titration period, 23 patients withdrew because of adverse events. The most commonly reported adverse events during the maintenance period of the trial were insomnia, nausea and falls.

The ASCEND-PD trial was a randomized, double-blind, two-treatment, 2-week crossover phase III study of CLERC and CLE (a combination treatment of carbidopa/levodopa and entacapone). Subjects taking a stable dose of CLE were converted to CLERC over a 6-week period. They were then randomly assigned to one of the two treatments (CLERC or CLE) for 2 weeks and were crossed over to the other treatment for an additional 2 weeks after a 1-week washout period. The study enrolled 110 subjects with advanced PD. Of these, 84 subjects completed the randomized double-blind comparative phase of the study. Following this phase, the subjects were enrolled into a 6-month open-label extension study. The study's primary endpoint was the percentage of "off time" during waking hours, as measured by patients' diaries. Patients entered the study with a baseline "off time" 5.9 hours. At the end of the randomized treatment phase, patients had an "off time" of 3.8 hours during waking hours compared with 5.2 hours with CLE. During double-blind treatment, 20.2% and 13.6% of patients reported adverse events on CLERC and CLE, respectively. The most common were dyskinesia, insomnia, and confusional state for CLERC, and fall for CLE.

The pharmacokinetic benefit of CLERC has been demonstrated in small trials. Hauser, et al compared CLERC with CD LD IR in an open label crossover study in 27 patients with advanced PD. Multiple-dose data showed IPX066 substantially reduced variability in plasma levodopa concentrations despite a lower dosing frequency (mean, 3.5 vs 5.4 administrations per day). In addition, total levodopa exposure during CLERC treatment was approximately 87% higher, whereas the increase in levodopa Cmax was approximately30% compared with CD LD IR.

Table 1- Summary of Clinical Trials for CLERC

Reference	Design, Study Population	Findings
APEX-PD	30 week , R,DB, PC in levodopa naïve patients 381 patients with early stage Parkinson's disease Fixed doses of CLERC, 145, 245, 390 mg TID	<table><tr><th></th><th>Placebo</th><th>145mg</th><th>245 mg</th><th>390 mg</th></tr><tr><td>UPDRS II</td><td>0.2</td><td>-2.8</td><td>-3.1</td><td>-3.9</td></tr><tr><td>UPDRS III</td><td>-0.7</td><td>-8.9</td><td>-9.8</td><td>-11.0</td></tr></table> Generally well tolerated and lower doses displayed less adverse events • Most common adverse events were nausea, headache, dizziness and insomnia. • Over all 10.2% of patients experienced adverse events that led to discontinuation
ADVANCE-PD	22 week, phase 3, R,DB, DD study assessing the efficacy of extended release carbidopa-levodopa in "off" time in patients with advanced Parkinson's Disease 393 patients were included in the mean efficacy analysis	<table><tr><th></th><th>CLERC</th><th>CD LD IR</th></tr><tr><td>Off time % waking day</td><td>-13.06%</td><td>-6.21%</td></tr><tr><td>responders</td><td>63%</td><td>45%</td></tr></table> There was a significant improvement in "on" time without bothersome dyskinesia's (0.8 hrs for CD LD IR and versus 1.9 hrs for CLERC) ($p<0.0001$) Most common adverse events: • Insomnia, nausea and falls
ASCEND-PD	11 week 2 part study. Part 1 was a R, DB, DD, 2 treatment 2 period cross over to assess safety and efficacy of CLERC versus CLE 84 patients completed the study	<table><tr><th></th><th>CLERC</th><th>CLE</th></tr><tr><td>Off time % waking day</td><td>-34%</td><td>-10%</td></tr></table> • An increase in "on" time with no troublesome dyskinesia's with CLERC (11.4 hrs) compared to CLE (10 hrs)

Potential Off-Label Use

Based on literature review, potential off-label uses of carbidopa/levodopa ER include the following:

- Treatment of restless leg syndrome
- Treatment of Cerebral palsy spasticity
- Treatment of chronic alcohol remission

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Hypersensitivity to carbidopa or levodopa • Narrow-angle glaucoma • Acute phase of MI • History of melanoma or undiagnosed pigmented lesions • Concurrent administration of nonselective monoamine oxidase inhibitors (e.g., phenelzine and tranylcypromine) or use within the past 2 weeks.
Warnings/Precautions	• History of MI with residual arrhythmias, peptic ulcer, or seizure • Severe cardiovascular, pulmonary, renal, hepatic, or endocrine disease; monitor disease parameters • Bronchial asthma patients taking sympathomimetics • Levodopa may cause patients to fall asleep while engaging in activities of daily living; caution regarding use of machinery and driving • Increased risk for hallucinations and psychosis when taking levodopa; other psychiatric symptoms include decreased impulse control and compulsive behaviors, depression, and suicidality • May exacerbate dyskinesia; reduce dose to control symptoms • Generalized polyneuropathy reported • Orthostatic hypotension may occur (more common with immediate-release formulation) • Open-angle glaucoma • Observe patients carefully if discontinued abruptly; risk of syndrome resembling neuroleptic malignant syndrome

Safety Considerations

Table 2 Adverse Events: APEX-PD

Adverse Event	Placebo (n=92) %	CLERC 36.25/ 145 mg TID (n=87) %	CLERC 61.25/245 mg TID (n=104) %	CLERC 97.5/ 390 mg TID (n=98) %
Nausea	9	14	19	20
Dizziness	5	9	19	12
Headache	11	7	13	17
Insomnia	3	2	9	6
Abnormal Dreams	0	2	6	5
Dry Mouth	1	3	2	7
Dyskinesia	0	2	4	5
Anxiety	0	2	3	5
Constipation	1	2	6	2
Vomiting	3	2	2	5
Orthostatic hypotension	1	1	1	5

Table 3 Adverse Events: ADVANCE-PD

Randomized Treatment	CLERC (N=201)		CD LD IR	
	Dose Conversion (%)	Maintenance (%)	Dose Conversion (%)	Maintenance (%)
Nausea	**3**	**3**	**6**	**2**
Headache	5	1	3	2
Dyskinesia	4	2	4	1
Dizziness	1	2	4	1
Insomnia	2	3	2	1
Fall	2	3	3	2
Constipation	2	1	2	1
Diarrhea	0	2	2	1
Weight loss	0	2	0	0
Somnolence	2	1	0	0
Tremor	2	0	1	1

Table 4 Adverse Events: ASCEND-PD

Adverse Event	Dose conversion (n=110)	Randomized Crossover with Rytary (n=89)	Randomized Cross over with CL+E (n=88)	Open Label washout (n=89)
Nausea	8	1	0	0
Fall	3	1	2	0
Upper respiratory tract infection	3	0	0	0
Vomiting	3	1	0	0
Dyskinesia	1	4	0	1
Insomnia	1	3	0	0
Confused State	0	3	0	0

Adverse Reactions

Common adverse reactions	Nausea (8-20%), dizziness(5-19%), abdominal pain, dyskensia
Death/Serious adverse reactions	Atrial fibrillation, constipation, gastroenteritis, dehydration, hyperkalemia
Discontinuations due to adverse reactions	Low dose CLERC 5% to high dose CLERC 20%

Drug Interactions

Drug-Drug Interactions

- Monoamine Oxidase (MAO) Inhibitors-The use of nonselective MAO inhibitors with CLERC is contraindicated. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating therapy with CLERC
- The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with CLERC may be associated with orthostatic hypotension. Monitor patients who are taking these drugs concurrently.
- Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa. Monitor patients for worsening Parkinson's symptoms.
- Iron salts or multi-vitamins containing iron salts can form chelates with levodopa and carbidopa and can cause a reduction in the bioavailability. If iron salts or multi-vitamins containing iron salts are coadministered with CLERC, monitor patients for worsening Parkinson's symptoms.

Risk Evaluation

As of October 1, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• None • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Dosing and Administration

Dosage in Patients Naïve to Levodopa Therapy

The recommended starting dosage in levodopa-naïve patients is 23.75 mg / 95 mg taken orally three times a day for the first 3 days. On the fourth day of treatment, the dosage of CLERC may be increased to 36.25 mg / 145 mg taken three times a day.

Based upon individual patient clinical response and tolerability, the dose may be increased up to a maximum recommended dose of 97.5 mg / 390 mg taken three times a day. The dosing frequency may be changed from three times a day to a maximum of five times a day if more frequent dosing is needed and if tolerated. The maximum recommended daily dose of CLERC is 612.5 mg / 2450 mg.

Converting from immediate-release (IR) to CLERC

Doses of other carbidopa/levodopa products are not interchangeable
For patients currently treated with carbidopa/levodopa plus catechol-O-methyl transferase (COMT) inhibitors (eg, entacapone), the initial total daily dose of levodopa in CLERC may need to be increased. The dosing frequency may be changed from 3x/day to a maximum of 5x/day if more frequent dosing is needed and if tolerated, up to a maximum recommended daily dose 612.5 mg/2450 mg

Dose conversion from IR 400-549 mg IR: 3 caps 23.75mg/95mg TID
550-749 mg IR: 4 caps 23.75mg/95mg TID
750-949 mg IR: 3 caps 36.25mg/145mg TID
950-1249 mg IR: 3 caps 48.75 mg/195 mg TID
≥1250 mg IR: 4 caps 48.75 mg/195 mg TID, OR 3 caps 61.25 mg/245 mg TID

Special Populations (Adults)

	Comments
Elderly	• In controlled clinical trials of CLERC, 418 patients were 65 years or older and no overall differences in safety and efficacy were observed between these patients and those under 65 years of age. • Use with caution in elderly patients; may be more sensitive to CNS effects (eg, hallucinations) of levodopa
Pregnancy	• Pregnancy risk category C • Adverse events have been observed in some animal reproduction studies using this combination. Carbidopa can be detected in the umbilical cord, but absorption in fetal tissue is minimal. Levodopa crosses the placenta and can be metabolized by the fetus and detected in fetal tissue
Lactation	• Levodopa is excreted in breast milk. A study was done in a single lactating woman at 4.5 months postpartum who had been taking carbidopa/levodopa for several years. Regardless of the formulation (sustained release or immediate release) peak levodopa concentrations in the breast milk were found ~3 hours after the maternal dose and returned to baseline ~6 hours after the dose. The highest milk concentration (3.47 nmol/L) was found following the immediate-release tablet and this was 27% of the peak maternal plasma concentration (occurring 30 minutes after the dose) and ~40% of the simultaneous plasma concentration. The manufacturer recommends that caution be exercised when administering carbidopa/levodopa to nursing women.
Renal Impairment	• No data identified
Hepatic Impairment	• No data identified

Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Pharmacokinetic data and clinical data demonstrate advantages of CLERC over current preparations of CD/LD. Trials in levodopa naïve, early stage PD as well as advance stage PD patients had more 'on' time while taking fewer doses, compared with CD LD IR and CD LD E. The percentage of patients with adverse effects were similar between treatment groups and do not support any new or unusual adverse effect from CLERC therapy. The titration of CLERC therapy can be a lengthy process and must be tailored individually.
- The benefit of a smoother absorption and levodopa exposure with CLERC may be of significant benefit to patients who develop significant periods of "off" time using other levodopa preparations.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.