Clinical Policy: Carbidopa/Levodopa ER Capsules (Crexont, Rytary), Enteral Suspension (Duopa), IR Tablets (Dhivy), Foscarbidopa/Foslevodopa (Vyalev)

Reference Number: CP.PMN.238
Effective Date: 09.01.20
Last Review Date: 08.24
Line of Business: Commercial, HIM, Medicaid* Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Carbidopa/levodopa extended-release capsules (Crexont®, Rytary®), enteral suspension (Duopa®) and immediate-release tablets (Dhivy®) are combinations of carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid).

Foscarbidopa/foslevodopa (Vyalev™) is a produg combination of foscarbidopa (an aromatic amino acid decarboxylation inhibitor), and foslevodopa (an aromatic amino acid). Foscarbidopa and foslevodopa are converted in vivo to carbidopa and levodopa.

For **Medicaid line of business, if request is through pharmacy benefit, Dhivy may not require prior authorization.*

FDA Approved Indication(s)

Crexont, Rytary, and Dhivy are indicated for the treatment of Parkinson's disease (PD), post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Duopa and Vyalev are indicated for the treatment of motor fluctuations in patients with advanced PD.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Crexont, Rytary, Duopa, Dhivy, and Vyalev are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Request for Crexont or Rytary (must meet all)**:**

1. Diagnosis of PD or parkinsonism;
2. Request is for Crexont or Rytary;
3. Age ≥ 18 years;
4. Documented intolerance or contraindication* to carbidopa-levodopa sustained release tablets (Sinemet® CR) that would not apply to Crexont or Rytary;
   **Examples of acceptable intolerance or contraindications include inability to swallow pills or intolerance or contraindications to excipients in carbidopa-levodopa sustained released tablets. Note: Failure of carbidopa-levodopa sustained released tablets is NOT an acceptable rationale for use of Crexont or Rytary over Sinemet CR.*

5. Dose does not exceed any of the following (a or b):
   a. Crexont: carbidopa 525 mg/levodopa 2,100 mg per day;
   b. Rytary: carbidopa 612.5 mg/levodopa 2,450 mg per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Request for Duopa or Vyalev (must meet all)**:**
1. Diagnosis of PD;
2. Request is for Duopa or Vyalev;
3. Prescribed by or in consultation with neurologist;
4. Age ≥ 18 years;
5. Demonstrated a clear responsiveness to treatment with levodopa;
6. Member is experiencing one of the following (a or b):
   a. For Duopa, motor fluctuations for 3 hours or more of "off" time per waking day (*see Appendix D*);
   b. For Vyalev, motor fluctuations for 2 hours or more of "off" time per waking day (*see Appendix D);*
7. Failure of at least two anti-Parkinson agents from different therapeutic classes, unless clinically significant adverse effects are experienced or all are contraindicated:*
   a. MAO-B inhibitor: rasagiline;
   b. COMT inhibitor: entacapone (Comtan®/Stalevo®), tolcapone;
   c. Dopamine agonist: ropinirole/ropinirole ER, pramipexole/pramipexole ER;

   **Prior authorization may be required for the above agents*
8. For Duopa requests, placement of a procedurally-placed tube has been completed or is planned;
9. Dose does not exceed any of the following (a or b):
   a. Duopa: 2,000 mg of the levodopa component (one cassette) per day;
   b. Vyalev: 3,525 mg of the foslevodopa component per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Request for Dhivy (must meet all)**:**
1. Diagnosis of PD or parkinsonism;
2. Request is for Dhivy;
3. Age ≥ 18 years;
4. Member must use generic carbidopa-levodopa, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed carbidopa 200 mg/levodopa 800 mg per day.

Approval duration:
HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed any of the following (a, b, c, d, or e):
   a. Crexont: carbidopa 525 mg/levodopa 2,100 mg per day;
   b. Rytary: carbidopa 612.5 mg/levodopa 2,450 mg per day;
   c. Duopa: 2,000 mg of the levodopa component (one cassette) per day;
   d. Dhivy: carbidopa 200 mg/levodopa 800 mg per day;
   e. Vyalev: 3,525 mg of the foslevodopa component per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
COMT: catechol-O-methyl transferase
MAO: monoamine oxidase
PD: Parkinson's disease
TLD: total levodopa dosage

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
carbidopa-levodopa sustained released tablets (Sinemet® CR)	Patients not currently receiving levodopa: Initial: carbidopa 50 mg/levodopa 200 mg PO BID. Patients currently receiving levodopa: *Note: Levodopa must be discontinued at least 12 hours before starting carbidopa/levodopa therapy.* Initial: Sinemet CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage; usual initial dose in mild to moderate disease is carbidopa 50 mg/levodopa 200 mg BID. Patients converting from immediate-release (IR) formulation to controlled release: Initial: Dosage should be substituted at an amount that provides ~10% more of levodopa/day, depending on clinical response, dosage may need	Most patients are adequately controlled on doses that provide up to 1,600 mg/day of levodopa.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	to be increased to provide up to 30% more levodopa/day. Total calculated dosage is administered in divided doses at intervals ranging from 4 to 8 hours during waking hours. An interval of at least 3 days between dosage adjustments is recommended.	
COMT Inhibitors		
carbidopa/ levodopa/ entacapone (Stalevo®)	PO: Dose should be individualized based on therapeutic response; doses may be adjusted by changing strength or adjusting interval. Fractionated doses are not recommended and only 1 tablet should be given at each dosing interval.	1,200 mg/day of levodopa (divided doses)
entacapone (Comtan®)	PO: 200 mg with each dose of levodopa/carbidopa	1,600 mg/day (divided doses)
tolcapone (Tasmar®)	PO: 100 mg 3 times daily, as adjunct to levodopa/carbidopa	600 mg/day
MAO-B Inhibitors		
rasagiline (Azilect®)	PO: Monotherapy or adjunctive therapy (not including levodopa): 1 mg once daily. Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability.	1 mg/day
Dopamine Agonists		
pramipexole (Mirapex®)	PO: Initial dose: 0.125 mg 3 times daily, increase gradually every 5 to 7 days; maintenance (usual): 0.5 to 1.5 mg 3 times daily	4.5 mg/day (divided doses)
pramipexole ER (Mirapex® ER)	PO: Initial dose: 0.375 mg once daily; increase gradually not more frequently than every 5 to 7 days to 0.75 mg once daily and then, if necessary, by 0.75 mg per dose	4.5 mg/day
ropinirole (Requip®)	PO: Recommended starting dose: 0.25 mg 3 times/day. Based on individual patient response, the dosage should be titrated with weekly increments: Week 1: 0.25 mg 3 times/day; total daily dose: 0.75 mg; week 2: 0.5 mg 3 times/day; total daily dose: 1.5 mg; week 3: 0.75 mg 3 times/day; total daily dose: 2.25 mg; week 4: 1 mg 3 times/day; total daily dose: 3 mg. After week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total of 24 mg/day.	24 mg/day (divided doses)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ropinirole ER (Requip® ER)	PO: Initial dose: 2 mg once daily for 1 to 2 weeks, followed by increases of 2 mg/day at weekly or longer intervals based on therapeutic response and tolerability	24 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Concomitant use of nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, tranylcypromine) or have recently (within 2 weeks) taken a nonselective MAO inhibitor
  - *Dhivy only*: Known hypersensitivity to any component of Dhivy
- Boxed warning(s): none reported

Appendix D: General Information

- Off time/episodes represent a return of Parkinson's disease symptoms (bradykinesia, rest tremor or rigidity) when the L-dopa treatment effect wears off after each dosing interval.
- Parkinson's disease symptoms, resulting from too little levodopa (L-dopa), are in contrast with dyskinesia which typically results from too much L-dopa. The alterations between "on" time (the time when Parkinson's disease symptoms are successfully suppressed by L-dopa) and "off" time is known as "motor fluctuations".
- The addition of carbidopa to L-dopa prevents conversion of L-dopa to dopamine in the systemic circulation and liver.
- Duopa is infused over 16 hours daily into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) with the CADD®-Legacy 1400 portable infusion pump. For short term use, Duopa may be administered through naso-jejunal tube prior to PEG-J tube placement with observation of the patient's clinical response.
- Vyalev is administered as a subcutaneous infusion with Vyafuser pump over the patient's waking hours or may be administered for 24 hours.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Crexont	PD; parkinsonism	Levodopa-naïve patients: Starting dose is 35 mg/140 mg PO BID for the first 3 days. Thereafter, dosage may be increased gradually as needed to a maximum daily dosage of carbidopa 525 mg / levodopa 2,100 mg divided up to four times daily. Patients converting from immediate-release carbidopa/levodopa: See Table 1 of Prescriber	Carbidopa 525 mg / levodopa 2,100 mg per day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Information for instructions; dosages are not substitutable on a 1:1 basis.	
Rytary	PD; parkinsonism	Levodopa-naïve patients: Starting dose is 23.75 mg/95 mg PO TID; may increase to 36.25 mg/145 mg TID on the fourth day of treatment. Based on individual patient clinical response and tolerability, may increase dose up to carbidopa 97.5 mg/levodopa 390 mg TID; frequency of dosing may be increased to a maximum of 5 times daily if needed and tolerated. Patients converting from immediate-release carbidopa/levodopa: See Table 1 of Prescriber Information for instructions. Dosages of Rytary are not interchangeable with other carbidopa-levodopa products.	Carbidopa 612.5 mg /levodopa 2,450 mg per day
Duopa	Motor fluctuations in patients with advanced PD	Duopa is administered over a 16-hour infusion period. The daily dose is determined by individualized patient titration and composed of: • A morning dose • A continuous dose • Extra doses Maximum recommended daily dose of Duopa is 2,000 mg of the levodopa component (i.e., one cassette per day) administered over 16 hours. At the end of the daily 16-hour infusion, patients will disconnect the pump from the PEG-J and take their night-time dose of *oral* immediate-release carbidopa-levodopa tablets. Duopa is initiated in 3 steps: 1. Conversion of patients to oral immediate-release carbidopa-levodopa tablets in preparation for Duopa treatment. 2. Calculation and administration of the Duopa starting dose (morning dose and continuous dose) for Day 1. 3. Titration of the dose as needed based on individual clinical response and tolerability. Duopa has an extra dose function that can be used to manage acute "off" symptoms that are	2,000 mg of levodopa component per day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		not controlled by the morning dose and the continuous dose administered over 16 hours. The extra dose function should be set at 1 mL (20 mg of levodopa) when starting Duopa. If the amount of the extra dose needs to be adjusted, it is typically done in 0.2 mL increments. The extra dose frequency should be limited to one extra dose every 2 hours. Administration of frequent extra doses may cause or worsen dyskinesias.	
Dhivy	PD; parkinsonism	Levodopa-naïve patients: Starting dose is 25 mg/100 mg PO TID; may increase by 1 tablet daily or every other day as needed	Carbidopa 200 mg/levodopa 800 mg per day
Vyalev	Motor fluctuations in patients with advanced PD	Vyalev is administered as a subcutaneous infusion with Vyafuser pump over the patient's waking hours or may be administered for 24 hours. Vyalev base continuous dosage and hourly infusion rate is initiated in 4 steps: 1. Calculate the total levodopa dosage (TLD) for the levodopa-containing medications that Vyalev is replacing. All dosages should be converted to the equivalent dosage of immediate-release levodopa to obtain the TLD. 2. Determine the total daily dosage (mg) of Vyalev foslevodopa component by multiplying the TLD by 1.3. 3. Determine the total daily volume (mL) of Vyalev by dividing the total daily dosage (mg) of Vyalev by 240. 4. Determine the hourly base continuous infusion rate of Vyalev by dividing the total daily volume (mL) of Vyalev by the number of hours the patient is typically awake (e.g., 16 hours) or may be administered for 24 hours. The maximum recommended daily dosage of Vyalev is 3,525 mg of the foslevodopa component.	3,525 mg of foslevodopa component per day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		An optional loading dose can be administered either with Vyalev or patients can continue using oral immediate-release carbidopa/levodopa tablets. If Vyalev is used for the loading dose, multiple the first morning dose of oral immediate release levodopa by 1.3 and divide by 240 to determine the loading dose of Vyalev. Vyalev has an extra dose function that can be programmed to 1 of 5 options (see Prescribing Information). The "extra dose" feature is limited to no more than 1 extra dose per hour. If 2 or more extra doses are used by the patient during the 24-hour/day treatment period, a revision of the base continuous infusion rate should be considered.	

VI. Product Availability

Drug Name	Product Availability
Crexont (carbidopa/levodopa)	ER capsules: carbidopa/levodopa 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, 87.5 mg/350 mg
Rytary (carbidopa/levodopa)	ER capsules: carbidopa/levodopa 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, 61.25 mg/245 mg
Duopa (carbidopa/levodopa)	Enteral suspension: 4.63 mg carbidopa and 20 mg levodopa per mL; each cassette contains approximately 100 mL of suspension; carton of 7 Duopa cassettes
Dhivy (carbidopa/levodopa)	IR tablets: carbidopa/levodopa 25 mg/100 mg; each tablet has 3 functional score with each segment containing 6.25 mg of carbidopa and 25 mg of levodopa
Vyalev (foscarbidopa/foslevodopa)	Single-dose vial: 12 mg foscarbidopa and 240 mg foslevodopa per mL; each vial contains approximately 10 mL of solution; carton of 7 Vyalev vials

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved policy CP.CPA.148; retire CP.CPA.148; added HIM and Medicaid lines of business; no significant changes from previously approved policy; references reviewed and updated.	04.27.20	08.20
3Q 2021 annual review: no significant changes; references revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	03.23.21	08.21
Added Duopa.	08.17.21	11.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less; RT4: added newly FDA approved product, Dhivy.	12.14.21	02.22
3Q 2022 annual review: no significant changes; references reviewed and updated.	03.25.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.06.22	
3Q 2023 annual review: no significant changes; consolidated continued therapy criteria for Rytary, Duopa and Dhivy to "All Indications in Section I"; references reviewed and updated.	04.20.23	08.23
3Q 2024 annual review: no significant changes; references reviewed and updated.	05.13.24	08.24
RT4: added newly approved Crexont to the policy.	08.19.24	
RT4: added newly approved Vyalev to the policy.	10.24.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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