Drugs for Parkinson’s disease:

**RYTARY™** (carbidopa and levodopa) extended-release oral capsule  
**TASMAR®** (tolcapone) oral tablet  
**ZELAPAR** (selegiline hydrochloride) orally disintegrating tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

**Description:**

Rytary (carbidopa/levodopa) extended release capsule is indicated for the treatment of Parkinson’s disease (PD), post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. Tasmar (tolcapone) tablet is indicated as an adjunct to Carbidopa and Levodopa for the treatment of signs and symptoms of idiopathic PD in patients who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies. Zelapar (selegiline) oral disintegrating tablet is indicated as an adjunct in the management of patients with PD being treated with Carbidopa/ Levodopa who exhibit deterioration in the quality of their response to this therapy.

Motor symptoms of PD are caused by a progressive degeneration of Dopamine (DA) containing neurons in the brain. Non-motor manifestations such as cognitive and psychiatric symptoms are thought to be due to
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

degeneration of other neurotransmitter systems within the brain. Degeneration of the DA neurons leads to DA deficiency and as a result the development of the classic triad of motor symptoms of resting tremor, muscle rigidity and bradykinesia. With the development of DA deficiency, there is also a relative excess of acetylcholine activity.

Drug therapy is targeted at reducing symptoms by enhancing the effects of DA or inhibiting the effects of acetylcholine. Levodopa has been long recognized in clinical practice guidelines and texts as the standard of care for PD. It is a precursor of DA and is able to cross the blood brain barrier where it is converted to DA. Levodopa is thought to be protective against the dopaminergic neuron damage observed in PD. Levodopa is converted to DA in the periphery before it is able to cross the blood brain barrier resulting in gastrointestinal adverse effects and a lower than expected concentration of Levodopa within the brain. To avoid this, Levodopa is combined with Carbidopa resulting in a decrease in the peripheral conversion of Levodopa to DA and allowing for more Levodopa to reach the brain to then be converted to DA. The combination of Carbidopa/Levodopa is one of the most effective treatments available for symptomatic relief of PD.

Other treatments include DA receptor agonists, catechol-O-methyl-transferase (COMT) inhibitors, selective monoamine oxidase type-B (MAOI-B) inhibitors, Amantadine, and selective use of anticholinergic agents. These agents are effective and safe in controlling motor symptoms in patients with advanced PD when used as adjunctive treatment to Levodopa. There is insufficient evidence to conclude that any one of these medications is clinically superior to another and there is insufficient evidence that shows one PD medication as superior to another in terms of improvement in functional outcomes.

Low cost generic options are available in immediate and extended-release formulations of Carbidopa/Levodopa as well as for each class of adjunctive therapy and are sufficient to meet the needs of most patients.

Definitions:

<table>
<thead>
<tr>
<th>Oral Anti-Parkinson’s disease agents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa</td>
<td>Carbidopa generic tabs</td>
</tr>
<tr>
<td></td>
<td>Lodosyn tabs</td>
</tr>
<tr>
<td>Carbidopa + Levodopa</td>
<td>Carbidopa + Levodopa – immediate release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Carbidopa + Levodopa ER – extended release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Carbidopa + Levodopa – ODT generic tabs</td>
</tr>
<tr>
<td></td>
<td>Rytary – extended release caps</td>
</tr>
<tr>
<td></td>
<td>Sinemet – immediate release tabs</td>
</tr>
<tr>
<td></td>
<td>Sinemet CR – extended release tabs</td>
</tr>
<tr>
<td>Carbidopa + Levodopa + Entacapone</td>
<td>Carbidopa + Levodopa + Entacapone generic tabs</td>
</tr>
<tr>
<td></td>
<td>Stalevo tabs</td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>Entacapone generic tabs</td>
</tr>
<tr>
<td></td>
<td>Comtan (entacapone) tabs</td>
</tr>
<tr>
<td></td>
<td>Tolcapone generic tabs</td>
</tr>
<tr>
<td></td>
<td>Tasmar (tolcapone) tabs</td>
</tr>
</tbody>
</table>
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

<table>
<thead>
<tr>
<th>MAO-B inhibitors</th>
<th>Selegiline generic tabs and caps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eldedryl (selegiline) caps</td>
</tr>
<tr>
<td></td>
<td>Zelapar (selegiline) – ODT tab</td>
</tr>
<tr>
<td></td>
<td>Azelect (rasagiline) tabs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DA agonists</th>
<th>Bromocriptine generic tabs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parlodel (bromocriptine) tabs</td>
</tr>
<tr>
<td></td>
<td>Pramipexole – immediate release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Pramipexole ER – extended release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Mirapex (pramipexole) – immediate release tabs</td>
</tr>
<tr>
<td></td>
<td>Mirapex ER (pramipexole) – extended release tabs</td>
</tr>
<tr>
<td></td>
<td>Ropinirole – immediate release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Ropinirole ER – extended release generic tabs</td>
</tr>
<tr>
<td></td>
<td>Requip – immediate release tabs</td>
</tr>
<tr>
<td></td>
<td>Requip XL – extended release tabs</td>
</tr>
</tbody>
</table>

The Child-Pugh classification system:

<table>
<thead>
<tr>
<th></th>
<th>Score: 1 point</th>
<th>Score: 2 points</th>
<th>Score: 3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>3.0 - 3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Serum Bilirubin (mg/dL)</td>
<td>&lt;2.0</td>
<td>2.0 - 3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>1 - 4</td>
<td>4 - 6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>moderate</td>
<td>severe</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>mild</td>
<td>severe</td>
</tr>
</tbody>
</table>

The three classes and their scores are:
- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

**Drug related events:**

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet

Information about medications that require precertification is available at www.azblue.com/pharmacy.
Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:
Rytary (carbidopa-levodopa) ER oral capsule

See “Resources” section for FDA-approved dosage.

- Precertification for Rytary (carbidopa-levodopa) ER oral capsule requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved dosage of Rytary (carbidopa-levodopa) ER oral capsule is considered medically necessary when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Medical record documentation of a confirmed diagnosis of ONE of the following:
     - Parkinson’s disease
     - Post-encephalitic parkinsonism
     - Parkinsonism following carbon monoxide intoxication
     - Parkinsonism following manganese intoxication
  3. Individual is unable to simultaneously use generic immediate-release Carbidopa/Levodopa AND generic extended-release Carbidopa/Levodopa tablets due to ONE of the following:
     - Experienced breakthrough symptoms of Parkinson’s disease
     - Had an intolerant adverse drug reaction to generic extended-release Carbidopa/Levodopa
  4. Absence of ALL of the following contraindications:
     - Use with or within 14 days of stopping Phenelezine
     - Use with or within 14 days of stopping Tranylcypromine
  5. Absence of ALL of the following exclusions:
     - Pregnancy
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

- Rytary (carbidopa-levodopa) ER oral capsule for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

**Criteria:**
Tasmar (tolcapone) oral tablet

See “Resources” section for FDA-approved dosage.

- Precertification for Tasmar (tolcapone) oral tablet requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved dosage of Tasmar (tolcapone) oral tablet is considered *medically necessary* as an adjunct to Carbidopa and Levodopa for the treatment of the signs and symptoms of idiopathic Parkinson’s disease when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Requires continued use of Carbidopa and Levodopa
  3. Unable to use ALL of the following due to condition failed to improve or worsened, or experienced a significant adverse drug reaction:
     - Carbidopa/Levodopa with generic tolcapone
     - Carbidopa/Levodopa with generic entacapone
     - Carbidopa/Levodopa with brand Comtan (entacapone)
     - Carbidopa/Levodopa/Entacapone generic
     - Stalevo (Carbidopa/Levodopa/Entacapone)
  4. ALL of the following baseline tests have been completed before initiation of treatment:
     - Liver enzyme tests
  5. Absence of ALL of the following contraindications:
     - Liver disease
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

- Aspartate transaminase or alanine transaminase are greater than upper limit of normal on two occasions
- Non-traumatic rhabdomyolysis
- Hyperpyrexia and confusion related to medication

6. Absence of ALL of the following exclusions:
   - Use with or within 14 days of stopping Phenelezine
   - Use with or within 14 days of stopping Tranylcypromine

➢ Tasmur (tolcapone) oral tablet for all other indications not previously listed is considered experimental or investigational based upon:
   1. Lack of final approval from the Food and Drug Administration, and
   2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
   3. Insufficient evidence to support improvement of the net health outcome, and
   4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
   5. Insufficient evidence to support improvement outside the investigational setting.

Criteria:
Zelapar (selegiline hydrochloride) orally disintegrating tablet

See “Resources” section for FDA-approved dosage.

➢ Precertification for Zelapar (selegiline) orally disintegrating tablet requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

➢ FDA-approved dosage of Zelapar (selegiline hydrochloride) orally disintegrating tablet is considered medically necessary as an adjunct in the management of patients with Parkinson’s disease being treated with Carbidopa/Levodopa who exhibit deterioration in the quality of their response to this therapy when ALL of the following criteria are met:
   1. Individual is 18 years of age or older
   2. Requires continued use of Carbidopa and Levodopa
   3. Unable to use generic selegiline tablet AND generic selegiline capsule due to ANY of the following:
      - Condition did not improve or worsened
Drugs for Parkinson’s disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

- Individual experienced a significant adverse drug reaction

4. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Liver function tests
   - Complete metabolic panel

5. Absence of **ALL** of the following contraindications:
   - Hypersensitivity to Selegiline
   - Concurrent use with Cyclobenzaprine
   - Concurrent use with Dextromethorphan
   - Concurrent use with St. John's wort
   - Concurrent use with or within 14 days of stopping ANY of the following:
     - Methadone
     - Meperidine
     - Propoxyphene
     - Tramadol
     - Phenelezine
     - Tranylcypromine
     - Azilect (rasagiline)
     - Other Selegiline products

6. Absence of **ALL** of the following exclusions:
   - Concurrent use with or within 14 days of stopping any antidepressant
   - Use within 5 weeks of stopping Fluoxetine
   - Severe hepatic impairment (Child-Pugh score > 9)
   - Severe renal impairment (creatinine clearance < 30 mL/min)
   - End-stage renal disease

- Zelapar (selegiline hydrochloride) orally disintegrating tablet for all other indications not previously listed is considered **experimental or investigational** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.
Drugs for Parkinson's disease:
RYTARY™ (carbidopa and levodopa) extended-release oral capsule
TASMAR® (tolcapone) oral tablet
ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)

Resources:

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| RYTARY 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 parkinsonism that may follow carbon monoxide intoxication or manganese intoxication | - Levodopa-naïve patients: Starting dose is 23.75 mg / 95 mg three times daily; may increase to 36.25 mg / 145 mg three times daily on the fourth day of treatment
- See Table 1 for instructions for converting patients taking immediate-release carbidopa-levodopa to RYTARY; dosages of RYTARY are not interchangeable with other carbidopa-levodopa products
- The maximum recommended daily dose of RYTARY is 612.5mg / 2450mg
- RYTARY may be taken with or without food; do not chew, divide or crush |

<table>
<thead>
<tr>
<th>Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa</th>
<th>Recommended Starting Dosage of RYTARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg to 549 mg</td>
<td>855 mg 3 capsules RYTARY 23.75 mg / 95 mg taken TID</td>
</tr>
<tr>
<td>550 mg to 749 mg</td>
<td>1140 mg 4 capsules RYTARY 23.75 mg / 95 mg taken TID</td>
</tr>
<tr>
<td>750 mg to 949 mg</td>
<td>1305 mg 3 capsules RYTARY 36.25 mg / 145 mg taken TID</td>
</tr>
<tr>
<td>950 mg to 1249 mg</td>
<td>1755 mg 3 capsules RYTARY 48.75 mg / 195 mg taken TID</td>
</tr>
<tr>
<td>Equal to or greater than 1250 mg</td>
<td>2340 mg or 2205 mg 4 capsules RYTARY 48.75 mg / 195 mg taken TID or 3 capsules RYTARY 61.25 mg / 245 mg taken TID</td>
</tr>
</tbody>
</table>
**Drugs for Parkinson’s disease:**

<table>
<thead>
<tr>
<th>RYTARY™ (carbidopa and levodopa) extended-release oral capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASMAR® (tolcapone) oral tablet</td>
</tr>
<tr>
<td>ZELAPAR (selegiline hydrochloride) orally disintegrating tablet (cont.)</td>
</tr>
</tbody>
</table>

**TASMAR** is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson’s disease.

Because of the risk of potentially fatal, acute fulminant liver failure, TASMAR (tolcapone) should ordinarily be used in patients with Parkinson’s disease on L-dopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies.

Because of the risk of liver injury and because TASMAR, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from TASMAR.

- Only prescribe TASMAR for patients taking concomitant carbidopa levodopa therapy
- The initial dose of TASMAR is always 100 mg three times per day. The recommended daily dose of TASMAR is also 100 mg three times per day. Elevations in ALT occurred more frequently at the dose of 200 mg three times per day
- If a patient fails to show the expected incremental benefit on the 200 mg dose after a total of 3 weeks of treatment (regardless of dose), TASMAR should be discontinued
- The first dose of the day of TASMAR was always taken together with the first dose of the day of levodopa/carbidopa, and the subsequent doses of TASMAR were given approximately 6 and 12 hours later
- TASMAR can be combined with both the immediate and sustained release formulations of levodopa/carbidopa. TASMAR may be taken with or without food
- TASMAR therapy should not be initiated in any patient with liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal

**ZELAPAR**, a monoamine oxidase type B (MAO-B) inhibitor, is indicated as an adjunct in the management of patients with Parkinson’s disease being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy

- Initiate treatment with 1.25 mg given once a day for at least 6 weeks; after 6 weeks, the dose may be escalated to 2.5 mg once a day
- ZELAPAR daily dose should not exceed 2.5 mg once daily
- Place tablet on top of the tongue where the tablet will disintegrate in seconds; avoid food and liquid intake 5 minutes before and after each dose
- In patients with mild or moderate hepatic impairment, the dose should be reduced to 1.25 mg; ZELAPAR is not recommended in patients with severe (Child-Pugh score >9) hepatic impairment