Drug Monograph

Perseris® (risperidone) Extended-Release Injection / Long Acting Injectable Atypical Antipsychotics

Drug/Drug Class:

Prepared for: MO HealthNet
Prepared by: Conduent

☑ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:
The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.

Perseris® is available as an extended-release injectable suspension containing either 90 mg or 120 mg risperidone. Each single-dose Perseris® kit contains: one sterile syringe prefilled with risperidone powder, one sterile syringe prefilled with the delivery system and one 18-gauge, 5/8-inch sterile safety needle for subcutaneous injection.

Distributed by: Indivior Inc., North Chesterfield, VA 23235

Perseris® is the first once-monthly subcutaneous risperidone-containing, long-acting injectable for the treatment of schizophrenia in adults. The efficacy of Perseris® was evaluated in a Phase 3 randomized, double-blind, placebo-controlled, 8-week study of 354 patients. Perseris® efficacy was demonstrated by an improvement in the primary clinical endpoint, Positive and Negative Syndrome Scale (PANSS) total score at day 57.

Status Recommendation:
☐ Prior Authorization (PA) Required ☑ Clinical Edit ☐ Open Access ☐ PDL

Type of PA Criteria:
☐ Increased Risk of ADE ☑ Appropriate Indications ☐ Non-Preferred Agent ☐ No PA Required
**Purpose**

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

**Introduction**

Schizophrenia is a chronic brain disorder that affects less than one percent of the U.S. population. When schizophrenia is active, symptoms can include delusions, hallucinations and extremely disordered thinking and behavior that impairs daily functioning. People with schizophrenia require lifelong treatment. Early treatment may help get symptoms under control before serious complications develop and may help improve the long-term outlook, however, treatment adherence is a major challenge due to the complexity of the disease.

**Dosage Form**

Perseris® is available as an extended-release injectable suspension containing either 90 mg or 120 mg risperidone. Each single-dose Perseris® kit contains: one sterile syringe prefilled with risperidone powder, one sterile syringe prefilled with the delivery system and one 18-gauge, 5/8-inch sterile safety needle for subcutaneous injection.

**Manufacturer**

Distributed by: Indivior Inc., North Chesterfield, VA 23235.

**Indication(s)**

Perseris® is indicated for the treatment of schizophrenia in adults.

**Clinical Efficacy**

The mechanism of action of risperidone, in schizophrenia, is unclear. The drug’s therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (paliperidone). Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Pharmacokinetics:

<table>
<thead>
<tr>
<th></th>
<th>Perseris®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>$T_{\text{max}}$ at 4 to 6 hours and at 10 to 14 days</td>
</tr>
<tr>
<td><strong>Volume of Distribution</strong></td>
<td>Large</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>90% (risperidone), 77% (9-hydroxyrisperidone)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic, primarily CYP2D6</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Urine 70%, Feces 14%</td>
</tr>
<tr>
<td></td>
<td>Renal Clearance 0.96 L/hr</td>
</tr>
</tbody>
</table>
**Clinical Trial:**

<table>
<thead>
<tr>
<th><strong>STUDY DESIGN</strong></th>
<th>8-week, randomized, double-blind, placebo-controlled study (N=354).</th>
</tr>
</thead>
</table>
| **INCLUSION CRITERIA** | Adults (age 18 to 55 years) experiencing acute exacerbations of schizophrenia.  
A Positive and Negative Syndrome Scale (PANSS) total score of 80 to 120 inclusive (moderate to severely ill) at screening visit. |
| **EXCLUSION CRITERIA** | Subjects who have an improvement in their total Positive and Negative Syndrome Scale (PANSS) score of 20% or greater between the initial screening visit and the first day of treatment.  
Subjects taking daily oral risperidone at a dose ≥ 6 mg/day.  
Subjects who have received a depot antipsychotic within 120 days of screen.  
Subjects with treatment resistant schizophrenia. |
| **TREATMENT REGIMEN** | Patients were randomized to receive two doses of Perseris® (90 mg or 120 mg) or placebo 28 days apart. |
| **RESULTS** | The primary endpoint was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the study (day 57).  
Both doses of Perseris® demonstrated a statistically significant improvement in the PANSS total score vs. placebo (Perseris 90 mg vs. placebo: difference = -6.50 [95% CI: -10.87, -2.13]; Perseris 120 mg vs. placebo: difference = -10.24 [95% CI: -14.64, -5.85]). |
| **SAFETY** | The most common adverse reactions (≥ 5% and greater than twice placebo) with Perseris® use were increased weight, sedation/somnolence, and musculoskeletal pain. |

**Contraindications**

Perseris® is contraindicated in patients with a known hypersensitivity to risperidone, its metabolite, paliperidone, or to any of its components

**Warnings and Precautions**

- **Black Box Warning** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Perseris® is not approved for the
treatment of patients with dementia related psychosis and has not been studied in this population.

- Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in elderly patients with dementia-related psychosis. Perseris® is not approved for the treatment of patients with dementia-related psychosis.
- Neuroleptic Malignant Syndrome has been reported in association with antipsychotic drugs. Manage with immediate discontinuation and close monitoring.
- Potentially irreversible tardive dyskinesia may occur. Risk increases with increased duration of therapy or higher total cumulative doses. Discontinue if clinically appropriate.
- Dyslipidemia and weight gain, which may increase cardiovascular or cerebrovascular risk, have been reported. Monitoring is recommended.
- Hyperglycemia, with some extreme cases associated with ketoacidosis, hyperosmolar coma or death have been reported with atypical antipsychotic use. Monitoring is recommended.
- Patients with diabetes mellitus or risk factors, including obesity and family history, are at an increased risk of worsening of glucose control or severe hyperglycemia. Monitoring is recommended.
- Hyperprolactinemia may occur and may result in galactorrhea, amenorrhea and gynecomastia. Patients with longstanding hyperprolactinemia may experience impotence, hypogonadism and decreased bone density.
- Use caution in patients with cardiovascular or cerebrovascular disease or conditions that predispose to hypotension, including dehydration, hypovolemia and antihypertensive medications due to increased risk of orthostatic hypotension. Monitor heart rate and blood pressure in these patients.
- Falls that may lead to fracture or other fall-related injuries may occur as a result of somnolence, postural hypotension or motor or sensory instability. Assessment of fall risk is recommended.
- Agranulocytosis, leukopenia and neutropenia have been reported, especially with preexisting low WBC and history of drug-induced leukopenia or neutropenia. Monitoring is recommended and discontinue if significant WBC decline or if patient have severe neutropenia.
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery.
- Seizures have been observed. Use caution in patients with a history of seizures or other conditions that potentially lower the seizure threshold.
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration. Use caution in patients at risk for aspiration pneumonia.
- Priapism has been reported and sever cases may require surgical intervention.
- Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported. Use caution in patients who will be exposed to temperature extremes.
- Renal or Hepatic Impairment: Carefully titrate on oral risperidone up to at least 3 mg before initiating treatment with Perseris® at a dose of 90 mg.
- Pregnancy: Treatment may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. There is a pregnancy registry that monitors pregnancy outcomes in women exposed to Perseris® during pregnancy.
- Fertility: Treatment with Perseris® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.
Adverse Effects

### Most common, ≥ 2%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Perseris® 90 mg (n=115) %</th>
<th>Perseris® 120 mg (n=117) %</th>
<th>Placebo (n=118) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>7.0</td>
<td>7.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2.6</td>
<td>2.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.7</td>
<td>2.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Weight increase</td>
<td>13.0</td>
<td>12.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>1.7</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.5</td>
<td>6.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0.9</td>
<td>7.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>5.2</td>
<td>5.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>2.6</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>7.0</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2.6</td>
<td>6.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>4.3</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.6</td>
<td>6.8</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Drug Interactions

The interactions of Perseris® with co-administration of other drugs have not been studied. The drug interaction data provided in this section is based on studies with oral risperidone.

- Concomitant use of Perseris® with strong CYP2D6 inhibitors may increase risperidone plasma concentration (examples: paroxetine, fluoxetine, quinidine).
- Concomitant use of Perseris® and a strong CYP3A4 inducer may decrease plasma concentrations of risperidone (examples: rifampin, carbamazepine, phenytoin, phenobarbital).
- Due to additive pharmacologic effects, the concomitant use of centrally-acting drugs, including alcohol, may increase nervous system disorders (examples: antipsychotics, alcohol).
- Because of its potential for inducing hypotension, Perseris® may enhance the hypotensive effects of other therapeutic agents with this potential (example: antihypertensives).
- Agents with central antidopaminergic activity such as Perseris® may antagonize the pharmacologic effects of dopamine agonists (examples: carbidopa, levodopa).
**Dosage and Administration**

The recommended dose of Perseris® is 90 mg or 120 mg administered once monthly by subcutaneous injection into the abdomen. Do not administer by any other route.

- Each injection must be administered by a healthcare professional using the prepackaged injection syringe and enclosed safety needle.
- For patients who have never taken risperidone, establish tolerability with oral risperidone prior to starting Perseris®.
- Do not administer more than one dose (90 mg or 120 mg total) per month.
- Neither a loading dose nor any supplemental oral risperidone is recommended.

**Cost**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Cost**/ month</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone</td>
<td>Perseris®</td>
<td>Indivior</td>
<td>90 mg or 120 mg SC once monthly</td>
<td>90 mg: $1,710.00 120 mg: $2,280.00</td>
</tr>
</tbody>
</table>

** Wholesale Acquisition Cost**

**Conclusion**

Perseris® is the first once monthly subcutaneous (SC) risperidone-containing, long-acting injectable. Clinically relevant levels are reached after the first injection of Perseris® without use of a loading dose or any supplemental oral risperidone. The safety and efficacy of Perseris® were evaluated in an 8-week, placebo-controlled study of 354 adult patients experiencing acute exacerbations of schizophrenia. The primary endpoint was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the study (day 57). Both doses of Perseris demonstrated a statistically significant improvement in the PANSS total score versus placebo. Similar to other atypical antipsychotic agents, Perseris® carries a boxed warning for increased mortality in elderly patients with dementia-related psychosis. The most common adverse reactions (≥ 5%) with Perseris® use were increased weight, sedation/somnolence, and musculoskeletal pain.

**Recommendation**

The Division recommends adding this drug to the current atypical antipsychotics clinical edit.

**References**
