Pharmacy Policy Bulletin

Title: Antipsychotic Agents
Policy #: Rx.01.163

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, gender or quantity restrictions. Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:
The intent of this policy is to communicate the medical necessity criteria for aripiprazole (Abilify®), asenapine (Saphris®), brexpiprazole (Rexulti®), cariprazine (Vraylar™), iloperidone (Fanapt®), lurasidone (Latuda®), paliperidone (Invega®), and pimavanserin (Nuplazid) as provided under the member’s pharmacy benefit.

Description:
Aripiprazole (Abilify) is an atypical antipsychotic indicated for the treatment of schizophrenia, acute treatment of manic and mixed episodes of bipolar I disorder, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and treatment of Tourette’s disorder. The exact mechanism of action of aripiprazole is unknown, but it is thought to occur through a combination of partial agonist activity through serotonin 5-HT1A and dopamine D2 receptors. Antagonistic activity may also occur through serotonin 5-HT2A receptors.

Asenapine (Saphris®) is an atypical antipsychotic indicated for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive therapy to lithium or valproate. The mechanism of action of asenapine, a dibenzo-oxepino pyrrole psychotropic is unknown. It has been suggested that the efficacy of asenapine in schizophrenia is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors.

Brexpiprazole (Rexulti®) is an atypical antipsychotic indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and for the treatment of schizophrenia. The exact mechanism of action of brexpiprazole is unknown, but it is thought to occur...
through a combination of partial agonist activity through serotonin 5-HT\textsubscript{1A} and dopamine D\textsubscript{2} receptors. Antagonistic activity may also occur through serotonin 5-HT\textsubscript{2A} receptors.

Cariprazine (Vraylar™) is an atypical antipsychotic indicated for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. The exact mechanism of action is unknown but is thought to be mediated through a combination of partial agonist activity at central dopamine D\textsubscript{2} and serotonin5-HT\textsubscript{1A} receptors and antagonist activity at serotonin 5-HT\textsubscript{2A} receptors.

Iloperidone is a psychotropic agent belonging to the chemical class of piperidinyl-benzisoxazole derivatives. The mechanism of action of iloperidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type 2 (D\textsubscript{2}) and serotonin type 2 (5-HT\textsubscript{2}) antagonisms. Iloperidone (Fanapt®) is indicated for the treatment of schizophrenia in adults.

Lurasidone is an atypical antipsychotic belonging to the chemical class of benzoisothiazole derivatives. Its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine type 2 (D\textsubscript{2}) and serotonin type 2 (5-HT\textsubscript{2}) receptor antagonism. Lurasidone (Latuda®) is indicated for the treatment of schizophrenia and for the treatment of depressive episodes associated with Bipolar I Disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.

Paliperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives and is the major active metabolite of risperidone. The mechanism of action of paliperidone is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine type 2 (D\textsubscript{2}) and serotonin type 2 (5-HT\textsubscript{2A}) receptor antagonism. Paliperidone (Invega®) is indicated for the treatment of schizoaffective disorder as monotherapy and as adjunct to mood stabilizers and/or antidepressants and for the treatment of schizophrenia.

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unknown. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent at serotonin 5-HT2C receptors. Pimvanaserin (Nuplazid) is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

**Policy:**

Aripiprazole (Abilify®), asenapine (Saphris®), cariprazine (Vraylar), iloperidone (Fanapt®), lurasidone (Latuda®), paliperidone (Invega®), and brexpiprazole (Rexulti®) are approved when there is documentation of ONE of the following:

1. Diagnosis of FDA approved indication for requested medication and inadequate response or inability to tolerate at least TWO of the following medications:
   a. Aripiprazole
   b. Clozapine
   c. Olanzapine
   d. Paliperidone
   e. Quetiapine
   f. Risperidone
   g. Ziprasidone
2. Documentation of continuous therapy with requested medication

Pimavanserin (Nuplazid) is approved when ALL of the following criteria are met:

A. Diagnosis of hallucinations and delusions associated with Parkinson's disease
B. Trial of dose adjustment or withdrawal of antiparkinson medications (anticholinergics, amantadine, dopamine agonists, COMT inhibitors, selegiline) prior to treatment with pimavanserin
C. Inadequate response or inability to tolerate clozapine or quetiapine

Black Box Warning:

Asenapine (Saphris), capriprazine (Vraylar), iloperidone (Fanapt), and paliperidone (Invega)

Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug, as opposed to some characteristic(s) of the patient, is not clear.

Aripiprazole (Abilify) and brexipiprazole (Rexulti)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole and brexipiprazole are not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short-term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. The safety and efficacy of aripiprazole and brexipiprazole have not been established in pediatric patients.

Lurasidone (Latuda)

Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Lurasidone is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and antidepressant drugs:

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients older than 24 years; there was a reduction in risk with antidepressant use in patients 65 years and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and
for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the health care provider.

**Pimavanserin (Nuplazid)**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Pimavanserin is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

**Guidelines:**
Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the pharmacy benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**


**Applicable Drugs:**
Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
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<tbody>
<tr>
<td>Saphris</td>
<td>asenapine</td>
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<tr>
<td>Vraylar</td>
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**Cross References:**

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**Policy Version Number:** 5.00

**P&T Approval Date:** October 13, 2016

**Policy Effective Date:** January 01, 2017

**Next Required Review Date:** July 14, 2017

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