Preferred Drug List

# NEW DRUG REVIEW

**Proprietary Name:** Saphris®

**Common Name:** Asenapine

**PDL Category: Antipsychotics-Atypicals**

| Comparable Products | Preferred Drug List Status |
|---|---|
| **Abilify®** | **Preferred** |
| **Risperidone** | **Preferred** |
| **Zyprexa®** | **Preferred** |

**Indications and Usage:** Acute treatment of schizophrenia in adults. Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[1]

**Mechanism of Action:** Exact mechanism of action is unknown. It has been suggested that the efficacy of Saphris® in schizophrenia is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors.[1]

**Metabolism:** The primary metabolic pathways include direct glucuronidation by UGTs and oxidative metabolism by the cytochrome P450 isoenzymes, predominantly CYP1A2. Therefore, careful use in combination with CYP1A2 inhibitors such as fluvoxamine is indicated. Asenapine is a weak inhibitor of CYP2D6 in vitro. Thus, combination of asenapine with either CYP2D6 substrates or inhibitors should be used with caution. It has been reported that use of asenapine may slightly increase the QTc interval ranging from 2 to 5msec when compared to placebo. It is therefore recommended that use of asenapine with other products that are known to prolong the QTc interval should be used cautiously. Additionally, it is recommended that use of asenapine should also be avoided in those with a history of cardiac arrhythmias and in conditions that may increase the risk of torsade de pointes.

**Dosage Forms:** Sublingual tablets: 5mg, 10mg.

**Recommended Dosage:** Schizophrenia: 5mg sublingually twice daily. Bipolar Disorder**:** 10 mg sublingually twice daily.[1] Dissolve 5-10mg under the tongue BID. No eating or drinking for ten minutes afterwards in order to be adequately absorbed into the bloodstream. Dosage adjustment is not required in patients with either renal or hepatic impairment although use is not recommended in severe hepatic impairment.

**Common Adverse Drug Reactions:** *All % for listed adverse events are given as the extent that they exceed placebo*. Constipation (0%), dry mouth (1%), oral hypoesthesia (4%), stomach discomfort (1%), vomiting (0%), fatigue (0%), irritability (>1%), increased appetite (>1%), increased weight (>2%), akathisia (3%), EPS (3%), dizziness (1%), somnolence (6%), insomnia (2%), and hypertension (0%). Tardive dyskinesia, a potentially irreversible movement disorder as well as NMS (neuroleptic malignant syndrome), have been reported with medications within this class of agents. With respect to weight gain, mean weight gain was 1.1kg for asenapine vs 0.1kg for placebo in short-term clinical trials compared with the mean difference for Abilify® was +0.7kg Abilify® vs -0.05kg for placebo. In a 52 week double blind RCT in patients with either schizophrenia or schizoaffective disorder 14.7 % of patients experienced weight gain ≥ 7 % body weight. Hyperglycemia, diabetes mellitus, and metabolic syndrome have been reported to occur in patients treated with atypical antipsychotics.

**Contraindications:** None[1]

**Manufacturer:** Schering-Plough Corporation

## Summary

**Analysis:** Saphris® is a new sublingual second generation antipsychotic belonging to the dibenzo-oxepino pyrroles class. This psychotropic agent is thought to have antagonistic activity at the $D_2$ and 5-$HT_{2A}$ receptors and has efficacy in the treatment of schizophrenia as well as the manic and mixed states of bipolar 1 disorder. Asenapine binds to many more receptors than other antipsychotics and strongly blocks dopamine type 1,2,3,4, as well as 5-HT1A, 5HT2A, 5HT2C, alpha1, and H1 receptors. As with all second-generation antipsychotics, Saphris® has a black box warning on the potential for increased mortality when used in elderly patients with dementia-related psychosis, with deaths being either cardiovascular or infectious in nature. When switching from another antipsychotic to Saphris®, the manufacturer recommends either an immediate or a gradual discontinuation of the previous treatment; however, it is recommended that in all instances, the overlapping period transitioning to the new antipsychotic be minimized. Because of this, duplicate therapy with other antipsychotics will only be allowed for a maximum of 30 days through point of sale (POS).

Three short-term randomized placebo- and active- controlled (haloperidol, risperidone, and olanzapine) clinical trials were performed to obtain FDA approval as treatment of schizophrenia. The primary endpoint for all three trials was a change from baseline on the PANSS total score. Saphris® was statistically superior to placebo for the treatment of schizophrenia symptoms in two of three trials and had a relapse rate of 12% after one year compared to placebo at 47%. Trials 1 and 2 showed asenapine 5mg twice a day to be statistically superior to placebo. However, asenapine 10mg twice a day did not show any added benefit compared to the 5mg twice a day dose in patients with schizophrenia. In the 3rd trial, asenapine was not found to be statistically superior to placebo. A major flaw in these studies was the exclusion of patients who failed other antipsychotics. This exclusion enriches the Saphris® efficacy trials with medication responders, thereby enhancing the probability of response. It is therefore unclear whether Saphris® has efficacy for treatment in resistant patients. As of the time of the writing of this analysis, data regarding 1200 patients in long term trials and 1500 in short term trials have not been published. The efficacy of asenapine (Saphris®) in bipolar disorder was demonstrated in two three-week double blind RCTs using improvement on the YMRS (Young Mania Rating Scale). In both trials, Saphris® was adjusted to 10 mg BID and the dose could be adjusted from 5 to 10 mg twice daily based on efficacy and tolerability. Saphris® was superior to placebo in both studies. Saphris® is a drug that needs to be taken twice a day and the patient needs to not eat or drink for ten minutes after each dose which can impose limitations on its use. On the other hand, the sublingual preparation may be an advantage for the small minority of patients who are unable to swallow pills.

It does not appear to offer any significant advantage in terms of efficacy. Its' side effect profile resembles a hybrid of Geodon due to the QTc prolongation risk and risperidone with EPS, weight gain and hyperprolactinemia. The mix of side effect profile differences might prove useful in certain patients. It would be advantageous if it proves to be less metabolically disturbing than Zyprexa.

Although this drug will not be suitable for many people due to its administration/absorption precaution it may be reasonable to provide the drug as a preferred cost-effective alternative on the PDL. It is not an ideal first line choice but it is also unlikely to be misused in this manner due to the drug's inherent limitations. It is recommended that Saphris® be added to the Preferred Drug List as a preferred drug with a POS duplicate therapy edit.

**IME Recommendation:**

☒ Preferred Drug with a POS duplicate therapy edit.
☐ Recommended Drug
☐ Non-Preferred Drug
☐ Non-Recommended Drug
☐ Preferred Drug with Conditions

1. Saphris® [package insert]. Kenilworth, NJ: Schering-Plough Corporation; 2009.
2. Medical Letter Volume 52, February 8, 2010