New Formulation – Asenapine Transdermal System (Secuado®)
FDA Approved October 2019
(Noven Pharmaceuticals, Inc.)

Indication: Asenapine transdermal system (TDS) is indicated for the treatment of adults with schizophrenia

Mechanism of Action: Asenapine displays a combination of antagonist activity at D_2 and 5-HT_{2A} receptors (exact mechanism of action is unclear)

Dosage & Administration

Dosage	• Initial: 3.8 mg/24 hrs • Range: 3.8 to 7.6 mg/24 hrs • Dose conversion between TDS & SL formulation ▪ asenapine TDS 3.8 mg/24 hrs corresponds to asenapine SL 5 mg BID ▪ asenapine TDS 7.6 mg/24 hrs corresponds to asenapine SL 10 mg BID
Hepatic impairment	• No dosage adjustment required in mild to moderate impairment • Contraindicated in pts with severe impairment (Child-Pugh C)
Administration	• Apply once daily to hip, abdomen, upper arm, or upper back area • Instruct clts to apply the patch to a different site each day to minimize skin reactions and to avoid exposing the patch to external heat sources during wear (may increase the rate & extent of absorption)
How Supplied	• 3.8 mg/24 hrs, 5.7 mg/24 hrs, & 7.6 mg/24 hrs transdermal system

DDI

Concomitant Medication	Effect
Paroxetine	Reduce paroxetine dose by half
Antihypertensive agents	Concomitant use may enhance antihypertensive effects. Monitor BP & adjust dosage of antihypertensives accordingly
Strong CYP1A2 Inhibitors	Consider asenapine TDS dose reduction based on clinical response

Pharmacokinetics

Absorption	~ 60% asenapine is released from the TDS over 24 hrs
Half-life elimination	~ 30 hrs following patch removal
Metabolism	• glucuronidation by UGT1A4 & oxidative metabolism by CYP 450 isoenzymes • pharmacological activity is primarily due to the parent drug
T_{max}	12 to 24 hrs
Steady state	attained in ~ 72 hrs after the first application
Inter-individual variability	~ 20 to 30%
Excretion	~ 50% in urine & 40% in feces

Adverse Effects

Most common (≥ 5% & at least twice that for placebo)	Extrapyramidal disorder, application site reaction, & weight gain
Other notable AEs (≥ 2% in any asenapine TDS dose group & which occurred at greater incidence vs. placebo)	Increased hepatic enzymes, headache, extrapyramidal symptoms, akathisia, somnolence, dystonia, & HTN
Dose-related adverse reactions	extrapyramidal disorder & weight gain

Warnings & Precautions

Black Box Warning: Increased mortality in elderly patients with dementia-related psychosis, not approved for the treatment of pts with dementia-related psychosis

Contraindication: Asenapine TDS is contraindicated in pts with severe hepatic impairment

Other warnings & precautions

• Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis • NMS • tardive dyskinesia • metabolic changes • orthostatic hypotension • falls • leukopenia, neutropenia, & agranulocytosis • QT prolongation • hyperprolactinemia • seizures • potential for cognitive & motor impairment • body temperature regulation • dysphagia • external heat • application site reactions

Clinical Studies

Efficacy

- The efficacy of asenapine TDS was established, in part on the basis of asenapine SL formulation trials. Additionally, the efficacy was evaluated in a 6-week, randomized, double-blind, fixed dose, placebo-controlled study of adult pts who met DSM-IV criteria for schizophrenia. 607 pts were randomized to receive asenapine TDS 3.8 mg/24 hrs, 7.6 mg/24 hrs, or placebo. The primary endpoint was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score to week 6 compared to placebo. Pts treated with asenapine TDS had statistically significant improvements in PANSS scores compared to placebo
- The change from baseline in the PANSS total score (placebo-subtracted difference) was
    - asenapine TDS 3.8 mg/24 hr group: -6.6 (95% CI: -9.81, -3.40)
    - asenapine TDS 7.6 mg/24 hr group: -4.8 (95% CI: -8.06, -1.64)
- Asenapine TDS also demonstrated statistically significant improvement in Clinical Global Impression-Severity (CGI-S) scores, the secondary endpoint of the Phase 3 study

Safety

- The safety of asenapine SL formulation, FDA approved in 2009, has been well-established
    - asenapine TDS safety profile was consistent with what is known for SL asenapine SL
- Please see the AEs section above
- The safety of asenapine TDS was evaluated in 315 adult pts with schizophrenia who were exposed to asenapine TDS for up to 6 weeks in a placebo-controlled trial
    - Akathisia was the most common AE that led to treatment discontinuation (0/204 pts in 3.6 mg/24 hrs, 3/204 pts in 7.8 mg/24 hrs, and 1/206 pts in the placebo group)
- Local skin reactions, such as irritation, were reported with asenapine TDS. During wear time or immediately after removal, the skin at the site of application may develop erythema, pruritus, papules, discomfort, pain, edema, or irritation. In the short-term, fixed-dose, placebo-controlled schizophrenia adult trial, application site reactions were reported in 15.2%of patients on 3.8 mg/24 hours and in 13.7% of patients on 7.6 mg/24 hours compared to 3.9% of placebo patients.

Role in Therapy

- Asenapine TDS, the first FDA approved atypical antipsychotic transdermal patch formulation, appears to be effective (study period 6 weeks) and offers a new formulation option for the treatment of schizophrenia
    - may enhance adherence for a subset of clts who dislike taking pills or find oral/injection formulations invasive
        - unlikely to substantially improve adherence
        - not long acting, require daily application of the patch
        - clts can still decide to stop the treatment on a daily basis (LAIs can last up to 3 months)
    - reduced dosing frequency compared to asenapine SL tabs (once daily vs BID), ease of use (no clinic visits compared to injections)

- improved tolerability compared to asenapine SL formulation (avoidance of hepatic first-pass metabolism → lower therapeutic doses/fewer AEs)
    - could be helpful for clts who experience GI side effects, have challenges swallowing tablets, or dislike the strange taste of SL tabs
- steady plasma drug concentration (avoidance of peaks & troughs associated with oral formulation)
- easier compliance monitoring

- However, transdermal formulation of an antipsychotic has only been recently marketed
    - blonanserin transdermal patch was recently approved in Japan
    - future studies should include a comparison of asenapine TDS with SL tablet and/or another antipsychotic
    - also, longer duration studies are needed to confirm asenapine TDS long term efficacy on the negative and positive symptoms of schizophrenia
- asenapine TDS has been marketed to offer easy supervision by the caregiver and an observable proof of treatment adherence
    - allows "non-intrusive, visual confirmation that a treatment is being utilized"
- asenapine SL tablet (Saphris®) is approved for the treatment of both schizophrenia and bipolar disorder
    - in a 52-week extension study in patients with bipolar mania, the efficacy of asenapine as maintenance treatment appeared comparable to olanzapine
    - a pooled analysis of 2 three weeks randomized trials of pts with major depression concurrent with mania (n=173) indicates remission occurred in more patients treated with asenapine (45%) than placebo (24%)
        - however, sedation, dizziness, EPS, & weight gain occurred more often with asenapine compared to placebo
    - Changes in blood pressure and heart rate are observed rarely with asenapine
- elevated risk (≥5%) of EPS, weight gain, and application site reaction
- intermediate rates of sedation
    - in the short-term, fixed-dose, placebo-controlled schizophrenia adult trial, somnolence was reported in 4.4% (9/204) of pts on asenapine TDS 3.8 mg/24 hrs and in 3.4% (7/204) of pts on 7.6 mg/24 hours compared to 1.5% (3/206) of pts on placebo
- asenapine TDS market availability is currently unknown

FDA-Approved Formulations of Asenapine

Generic (Brand)	Indication	Formulation	Dosage	Cost	Comments
Asenapine TDS (Secuado®)	Schizophrenia	Transdermal system	3.8 mg/24 hrs to 7.6 mg/24 hrs	$1200	• avoid exposing the patch to external heat sources during wear (may increase the rate & extent of absorption) *the skin at the site of application may develop erythema, pruritus, papules, discomfort, pain, edema, or irritation. *instruct patients to select a different application site each day to minimize skin reactions.

Asenapine (Saphris®)	Bipolar Disorder & Schizophrenia	Sublingual tabs	5-10 mg sublingually BID	$1200	• the most rapidly absorbed tab (Tmax 1 hr) • sensation of mouth numbness/strange taste • should be placed under the tongue & allowed to completely dissolve • NOT to be swallowed • avoid eating/drinking for at least 10 minutes post administration

Formulary Recommendation

Add to formulary with PA for CMC and BHRS

PA approval criteria:

- Medically accepted indications, and
- Tried and failed two generic atypical antipsychotics, and
- Inability to tolerate or nonadherence to oral or sublingual formulations, and

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