Secnidazole (Solosec™) New Drug Update

October 2017

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>secnidazole</th>
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<tbody>
<tr>
<td>Trade Name (Manufacturer):</td>
<td>Solosec (Symbiomix)</td>
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<td>Form:</td>
<td>Oral granules</td>
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<tr>
<td>Strength:</td>
<td>2 gram per unit-of-use child-resistant foil packet</td>
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<tr>
<td>FDA Approval:</td>
<td>September 15, 2017</td>
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<td>Market Availability:</td>
<td>Anticipated in first quarter 2018</td>
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<tr>
<td>FDA Approval Classification:</td>
<td>Priority Review</td>
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<tr>
<td>Classification:</td>
<td>Specific Therapeutic Class (HIC3): TBD</td>
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**INDICATION**

Secnidazole is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis (BV) in adult women.

Secnidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria in order to reduce the risk of drug-resistant bacteria. Culture and susceptibility information should be used when available; otherwise local epidemiology and susceptibility patterns may by used for empiric selection of therapy.

**CONTRAINDICATIONS/WARNINGS**

Secnidazole is contraindicated in patients with a hypersensitivity to any ingredient of the product or to other nitroimidazole derivatives.

Treatment with secnidazole may result in vulvovaginal candidiasis. Treatment with an antifungal agent may be required.

Animal studies have reported carcinogenicity with chronic use of nitroimidazole derivatives; therefore chronic use of secnidazole should be avoided.

Use of secnidazole without proven or strongly suspected bacterial infection or for prophylaxis is not likely to provide benefit and may increase the risk of development of drug-resistant bacteria.

**DRUG INTERACTIONS**

There are no reported clinically significant drug interactions reported with secnidazole. It is minimally metabolized by the CYP 450 enzyme system.
COMMON ADVERSE EFFECTS

In patients treated with secnidazole, the most common adverse reactions (≥ 2%) are vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), diarrhea (2.5%), abdominal pain (2%), and vulvovaginal pruritus (2%).

SPECIAL POPULATIONS

Pregnancy

Data for use in pregnant women are lacking to inform of drug-related adverse developmental effects; none were reported in animal studies with dosages 4 times greater than human dosage.

Pediatrics

Safety and efficacy have not been established in pediatric patients younger than 18 years of age.

Geriatrics

Clinical trials did not include adequate numbers of patients aged 65 and older to establish difference in response compared to younger individuals.

Renal/Hepatic Impairment

Secnidazole is minimally (≤ 1%) metabolized in the liver and approximately 15% of a dose is excreted unchanged in the urine. Dosage adjustments are not recommended for patients with renal or hepatic impairment.

DOSAGES

The recommended dose of secnidazole is a single oral 2 gram dose taken without regard to food. The entire content of the foil packet should be sprinkled onto applesauce, yogurt, or pudding. The entire mixture should be consumed within 30 minutes. Do not chew or crunch the granules. A glass of water may be taken after oral administration of secnidazole to aid in swallowing; however the granules are not intended to be dissolved in any liquid.

CLINICAL TRIALS\textsuperscript{2,3,4}

A literature search was performed using “secnidazole” and “bacterial vaginosis.”

The safety and efficacy of secnidazole was evaluated in a phase 3 placebo-controlled trial that included 189 non-pregnant women (ages 18 to 54) with a clinical diagnosis of BV based on Amsel criteria (off-white vaginal discharge, vaginal pH ≥ 4.7, clue cells [epithelial cells with adhering bacteria] ≥ 20% on microscopy of vaginal sample, and positive 10% KOH whiff test) and a Nugent score ≥ 4. Patients were randomized (2:1) to a single oral dose of secnidazole 2 g or placebo. The primary efficacy endpoint of clinical outcome response (COR) was defined as normal vaginal discharge, negative KOH whiff test, and clue cells < 20% assessed between days 21 to 30 after the study dose. The primary endpoint was reported using the modified intent-to-treat (mITT) population, which included all randomized patients who met entry criteria. COR was achieved in 53.3% of patients treated with secnidazole versus 19.3% with placebo (p<0.001) at days 21 to 30. In addition, in patients with a baseline Nugent score of 7 to 10, COR at day 7 to 14 was reported in 64% treated with secnidazole compared to 26.4% with placebo. A therapeutic
response, defined as a clinical response plus the secondary endpoint of Nugent score of ≤ 3, was reported in 34.6% of patients treated with secnidazole versus 3.5% treated with placebo. While the clinical response rates were lower in the subgroups of Black women (which was 54% of the study population) and in those with a history of ≥ 4 BV episodes in the 12 months preceding randomization, there was a treatment difference in favor of secnidazole in these subgroups.

Data from the pivotal phase 2 and 3 trials and an open-label single-arm safety trial report vulvovaginal candidiasis as the most commonly reported treatment emergent adverse event (9.6%) occurring with secnidazole. Other common adverse events were nausea, vomiting, diarrhea, abdominal pain, headache, and dysgeusia.

A multicenter, prospective, randomized (1:1), double-blind, double-dummy, phase 3 trial conducted in France was designed according to FDA guidelines to compare the efficacy of secnidazole with metronidazole in 577 non-pregnant women aged 18 to 65 years with clinical signs of BV. Clinical diagnosis of BV was established based on the Amsel criteria; the diagnosis was later confirmed by a Nugent score > 7 on bacteriological analysis of the preinclusion vaginal samples. Patients were randomized 1:1 to a single dose of oral secnidazole 2g or oral metronidazole 500 mg twice daily for 7 days. The primary efficacy endpoint was therapeutic success, which was a composite of clinical and bacteriological cure, at day 28; clinical cure was defined as normalization of the Amsel criteria, bacteriological cure was defined as Nugent score ≤ 3. The intent-to-treat (ITT) population included all patients who received at least 1 dose of study drug, modified ITT (mITT) population included all patients in the ITT who had a confirmed diagnosis of BV, and the per protocol (PP) population included mITT patients who completed the study protocol. BV was confirmed in 243 (84.7%) patients in the secnidazole group and 237 (81.7%) in the metronidazole group (mITT). The primary endpoint of therapeutic response was achieved at similar rates in patients treated with secnidazole or metronidazole, across all analysis populations (ITT 58.3% versus 57.8%, mITT 60.1% versus 59.5%, PP 63.4% versus 62.9%, respectively). Non-inferiority was achieved. Therapeutic success rates found at day 14 were consistent with rates reported at day 28. In addition, mean time to symptom disappearance in the mITT populations that completed self-assessment was 6.8 days with secnidazole (84.4% reported) and 7.1 days with metronidazole (82.4% reported). There were no differences in reported adverse events between the study drugs; however, headache was reported infrequently with both agents, but more often with secnidazole (n=10 versus n=4).

OTHER DRUGS USED FOR CONDITION

Therapies approved by the Food and Drug Administration (FDA) for the treatment of BV include oral or topical metronidazole, oral or topical clindamycin, and oral tinidazole (Tindamax®). Treatment durations range from 1 to 7 days. According to the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases (STD) 2015 Treatment Guidelines, the recommended regimens for the treatment of BV in pregnant or non-pregnant symptomatic women include oral metronidazole 500 mg (Flagyl®) twice daily for 7 days, metronidazole gel 0.75% (MetroGel-Vaginal®, Vandazole®) intravaginally once daily for 5 days, or clindamycin 2% cream (Cleocin®, Clindesse®) intravaginally at bedtime for 7 days. Alternatives include, oral tinidazole (2 g daily for 2 days or 1 gm daily for 5 days), clindamycin (300 mg twice daily for 7 days) or clindamycin intravaginal ovule (100 mg at bedtime for 3 days). The established benefits of therapy in nonpregnant women are to relieve signs and symptoms of infection. Data on the safety and efficacy on the treatment of asymptomatic BV in pregnant women who are at high- or low-risk of preterm delivery is conflicting.
PLACE IN THERAPY

The prevalence of BV is estimated to be 21.2 million (29.2%) among women ages 14 to 49 years in the United States. Asymptomatic cases, which occurs in approximately 84% of cases, may resolve without treatment; however, patients with symptoms should be evaluated and treated. If left untreated, patients may be at greater risk of contracting sexually transmitted infections, including HIV, herpes simplex, chlamydia, gonorrhea, and trichomoniasis and delivering preterm or low-birth weight infants.

Secnidazole (Solosec) is a 5-nitroimidazole with demonstrated in vitro activity against many anaerobic Gram-negative and Gram-positive bacteria, while sparing Lactobacillus species. It is the first single-dose agent for the treatment of BV in adult women. It is structurally similar to metronidazole and tinidazole, but has a longer half-life compared to either product (secnidazole, 17 hr; oral metronidazole, 8 hr; tinidazole, 12-14 hr). No dosage adjustment is needed with secnidazole in patients with severe hepatic impairment, unlike oral metronidazole that requires a 50% dose reduction in this population (caution should be used with topical metronidazole). Also, avoidance of alcohol consumption is not required with secnidazole, as with metronidazole and tinidazole.

While, use of a single-dose treatment option may increase adherence to therapy, this has not been established. The safety profile of secnidazole is similar to other 5-nitroimidazole agents. Although, resistance to secnidazole was not tested, some data suggests cross–resistance between secnidazole and metronidazole in vitro.

SUGGESTED UTILIZATION MANAGEMENT

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<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
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| Clinical Edit | • Clinical diagnosis bacterial vaginosis based on all of the following  
  o off-white/gray vaginal discharge  
  o vaginal pH ≥ 4.7  
  o clue cells ≥ 20% on microscopy  
  o positive 10% KOH whiff test  
  o Nugent score ≥ 4 on gram stain  
  • Female patients ≥ 18 years of age  
  • No hypersensitivity to nitroimidazole derivatives  
  • No in vitro resistance to nitroimidazole derivatives (metronidazole, tinidazole, secnidazole) or prior failure of metronidazole or tinidazole for the current course of infection |
| Quantity Limit | 1 packet |
| Duration of Approval | 1 day |
| Drug to Disease Hard Edit | None |

REFERENCES

1 Solosec [package insert], Newark, NJ; Symbiomix; September 2017.
2 Solosec [package insert], Newark, NJ; Symbiomix; September 2017.


10 Tindamax [package insert]. San Antonio, TX; Mission; February 2014.