NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplements
Application Numbers	NDA 209363/S-014 NDA 209363/S-016
Priority or Standard	Standard
Submit Dates	**NDA 209363/S-014:** March 29, 2021 **NDA 209363/S-016:** August 30, 2021
Received Dates	**NDA 209363/S-014:** March 29, 2021 **NDA 209363/S-016:** August 30, 2021
PDUFA Goal Dates	**NDA 209363/S-014:** January 29, 2022 **NDA 209363/S-016:** June 30, 2022
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	January 19, 2022
Established/Proper Name	secnidazole
Trade Name	SOLOSEC
Pharmacologic Class	Nitroimidazole
Applicant	Lupin Inc.
Dosage form	Granules
Applicant proposed Dosing Regimen	A single 2-gram packet of granules taken once orally
Applicant Proposed Indications/Populations	**NDA 209363/S-014:** Treatment of bacterial vaginosis in adolescent women 12 years of age and older **NDA 209363/S-016:** Treatment of trichomoniasis caused by *Trichomonas vaginalis* in adolescents 12 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	**NDA 209363/S-014:** 419760006 Bacterial vaginosis (disorder) **NDA 209363/S-016:** 276877003Trichomonal vaginitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	**NDA 209363/S-014:** Treatment of bacterial vaginosis in female patients 12 years of age and older **NDA 209363/S-016:** Treatment of trichomoniasis caused by *Trichomonas vaginalis* in patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	**NDA 209363/S-014:** 419760006 Bacterial vaginosis (disorder) **NDA 209363/S-016:** 276877003Trichomonal vaginitis (disorder)
Recommended Dosing Regimen	A single 2-gram packet of granules taken once orally

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BV	bacterial vaginosis
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HIV	human immunodeficiency virus
HSV	herpes simplex virus
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
sNDA	supplemental NDA
SOC	standard of care
STI	sexually transmitted infection
TEAE	treatment emergent adverse event
TOC	test of cure
TV	*Trichomonas vaginalis*
WR	Written Request

1 Executive Summary

1.1. Product Introduction

Secnidazole (SOLOSEC™) is an oral antimicrobial drug in the 5-nitroimidazole class that was initially approved in 2017 for the treatment of bacterial vaginosis (BV) in adult women 18 years of age and older. On June 30, 2021, the indication for treatment of trichomoniasis in adults 18 years of age and older was added. The supplemental NDAs (sNDAs) discussed in this submission propose to add pediatric indications for treatment of BV in female patients 12 years of age and older (S-014) and treatment of trichomoniasis in patients 12 years of age and older (S-016).

SOLOSEC is currently available as an oral granule formulation. The proposed regimen for BV in female patients 12 years of age and older and in trichomoniasis patients 12 years of age and older is the same as that approved for adults, namely a single 2-gram packet of granules taken once orally without regard to the timing of meals.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The benefit risk assessment for SOLOSEC is favorable for the treatment of BV in female pediatric patients aged 12 to less than 18 years. The pathogenesis of BV in adolescent patients is the same as that of adult patients; therefore, the efficacy data in previously reviewed controlled trials of SOLOSEC for treatment of BV in adults can be extrapolated to pediatric patients aged 12 to less than 18 years. The safety of secnidazole in the treatment of pediatric patients aged 12 to less than 18 years with BV is supported by a multicenter, uncontrolled, open-label study evaluating the safety and tolerability of a 2 g single dose of SOLOSEC in 40 female patients aged 12 to less than 18 years submitted in these efficacy supplements (study SYM-1219-401). The overall safety findings in this study are consistent with findings in adult BV patients aged 18 to 65 years old and support the safety of SOLOSEC for the treatment of BV in patients 12 years of age and older.

The benefit risk assessment for SOLOSEC is favorable for the treatment of trichomoniasis in pediatric patients aged 12 to less than 18 years. As in BV, the pathogenesis of trichomoniasis in adolescent patients is the same as that of adult patients; therefore, the efficacy data from the controlled trial of SOLOSEC for treatment of trichomoniasis in adult female patients can be extrapolated to pediatric female patients aged 12 to less than 18 years. Since trichomoniasis is a less severe disease in males than females and is often self-limited, the efficacy data from the controlled trial in females with supporting evidence from published studies of a single 2 g secnidazole dose for treatment of trichomoniasis in males have already been found sufficient to support the indication for the treatment of trichomoniasis in males [sNDA (S-012)]. As these trials included male patients aged 12 to less than 18 years, the efficacy of secnidazole can also be extrapolated to male patients 12 years of age and older.

The assessment of the safety of SOLOSEC for treatment of trichomoniasis in adolescent females is primarily based on the safety of SOLOSEC in adolescent females with BV demonstrated in study SYM-1219-401. To assess the safety of SOLOSEC for treatment of trichomoniasis in adolescent males, the reviewers evaluated data from study SYM-1219-401 in addition to safety data used to support the approval of SOLOSEC for treatment of adult males, including two Phase 1 studies that enrolled healthy male subjects and published studies of secnidazole treatment of trichomoniasis in males. In summary, the safety of SOLOSEC for treatment of trichomoniasis in adolescent female and male patients was found to be acceptable.

Of note, the indication for treatment of trichomoniasis in patients 12 years and older includes the simultaneous treatment of partners of infected patients in order to prevent reinfection.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Secnidazole (SOLOSEC™) is an oral antimicrobial drug in the 5-nitroimidazole class currently approved as a single 2 g dose for treatment of bacterial vaginosis (BV) in adult women and treatment of trichomoniasis caused by *Trichomonas vaginalis* (TV) in adults. The supplemental NDAs reviewed in this submission propose to expand the BV indication to female patients 12 years of age and older (S-014) and the trichomoniasis indication to female and male patients 12 years of age and older (S-016). The proposed dosing regimen for adolescents is the same as for adults for both indications. The submissions include data from a multicenter, uncontrolled, open-label study (SYM-1219-401) that evaluated the safety and tolerability of a 2 g single oral dose of SOLOSEC in 40 female patients aged 12 to less than 18 years with BV.

Efficacy

The pathophysiology of both BV and trichomoniasis is the same in adolescent and adult patients. Therefore, the determination of the effectiveness of SOLOSEC in the treatment of BV in adolescent females and trichomoniasis in adolescent females and males was based on extrapolation of efficacy data from the controlled clinical studies conducted in female adults for both indications, with supporting evidence from the published studies of trichomoniasis treatment in males. The efficacy results observed in the open-label, non-comparative study of SOLOSEC in adolescent females with BV (SYM-1219-401) were favorable and generally consistent with those observed in the adult SOLOSEC BV treatment trials.

Safety

The safety profile of SOLOSEC generated from 40 female patients aged 12 to less than 18 years treated for BV in study SYM-1219-401 was consistent with the previous safety findings for the treatment of BV in adults. No deaths, serious adverse events (SAE), or severe intensity adverse events were reported in study SYM-1219-401. For adolescent male trichomoniasis patients aged 12 to less than 18 years, assessment of safety was supported by the safety results of SYM-1219-401, clinical data in the initial NDA consisting of two safety/pharmacokinetic (PK) studies (SYM-1219-104 and SYM-1219-105) of SOLOSEC that included healthy adult male volunteers, and safety data available from published studies of the use of secnidazole in males; none of these sources revealed any significant safety signals.

In summary, the benefit-risk assessment of the information provided in these submissions supports the approval of SOLOSEC oral granules for the treatment of BV in female patients aged 12 to less than 18 years and trichomoniasis caused by TV in patients aged 12 to less than 18 years. The trichomoniasis indication also includes the simultaneous treatment of partners of infected patients to prevent reinfection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Bacterial vaginosis (BV) is a common cause of vaginitis in women of childbearing age. A change in the normal flora of the vagina caused by douching, taking antibacterials, using an intrauterine device, and/or unprotected sexual activity are associated with development of BV. There are epidemiological associations between BV and other adverse health outcomes such as human immunodeficiency virus (HIV) acquisition and preterm birth. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months. • Trichomoniasis is a sexually transmitted infection (STI) caused by the protozoa *Trichomonas vaginalis* (TV). It is estimated to be the most prevalent nonviral STI in United States adolescents and especially in adolescent females. For women, younger age at first sexual encounter, greater number of sex partners, and a history of chlamydia infection in the past 12 months are associated with TV infection. Trichomoniasis is often asymptomatic, especially in men, facilitating the transmission of the infection to sexual partners. In women, TV infection may be associated with vaginal itching, odor, and discharge. Males may experience urethritis. Untreated disease is associated with adverse reproductive health consequences such as cervical neoplasia, pelvic inflammatory disease, and infertility. Importantly, TV infection is associated with increased risk of acquisition of HIV, premature rupture of membranes, preterm birth, and delivery of low birthweight infants for gestational age. Infants born to infected mothers may become infected during delivery which may result in neonatal complications.	BV is a common cause of vaginitis in women of childbearing age associated with adverse health outcomes such as HIV acquisition and preterm birth. Trichomoniasis is the most prevalent nonviral STI in adolescents in the U.S. and is associated with adverse reproductive health and pregnancy outcomes and increased risk of acquisition of HIV.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The Centers for Disease Control and Prevention (CDC) recommended therapies for BV include oral or topical metronidazole, oral or topical clindamycin, oral tinidazole, or oral secnidazole. Of these, metronidazole vaginal gel 0.75% and 1.3%, and clindamycin vaginal suppositories are FDA approved for treatment of BV in adolescent patients. • The CDC recommended therapies for trichomoniasis include oral tinidazole 2 gram as a single dose, oral metronidazole 2 gram single dose, or oral metronidazole 500 mg twice a day for 7 days. There are no specific guidelines for adolescent patients. There are no drugs approved for treatment of trichomoniasis in adolescent patients.	A single dose oral therapy would provide a convenient option for adolescent females with BV and may potentially improve patient compliance compared to the current treatment options. A treatment option for trichomoniasis in adolescent patients is needed.
Benefit	• The determination of the effectiveness of SOLOSEC in the treatment of BV and trichomoniasis is primarily based on extrapolation of efficacy data from the controlled studies of treatment of BV and trichomoniasis conducted in female adults, as well as from published studies of secnidazole use for trichomoniasis treatment in adult and adolescent males. • The pathophysiology of BV and trichomoniasis in adolescent patients aged 12 to less than 18 years is the same as that of adult patients 18 years of age and older thus supporting extrapolation of adult effectiveness data to adolescents. • One clinical study (SYM-1219-401) was submitted to support the use of SOLOSEC in adolescent females for the treatment of BV. Although study SYM-1219-401 was primarily an observational safety study, some efficacy endpoints were evaluated at the test of cure (TOC) visit. The overall results observed in SYM-1219-401 in adolescents for SOLOSEC were	SOLOSEC, as a single dose oral therapy, is efficacious in treating BV and trichomoniasis in adolescent patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	favorable and generally consistent with those observed in the adult SOLOSEC phase 3 BV study, SYM-1219-301.	
Risk and Risk Management	• The overall rate of treatment emergent adverse events (TEAE) in the safety study (SYM-1219-401) in adolescent females with BV was 7.5% which was lower than the rates of TEAE in the adult BV and trichomoniasis treatment studies (29% and 14.9%, respectively). • In study SYM-1219-401, there were no deaths, serious AEs, or discontinuations due to AEs. • For adolescent males, assessment of safety was supported by the safety results of study SYM-1219-401, clinical data in the initial NDA consisting of two safety/PK studies (SYM-1219-104 and SYM-1219-105) with secnidazole that included healthy adult male volunteers, and safety data available from published studies of secnidazole use in males.	The risk profile of SOLOSEC is acceptable compared to the expected benefit and can be adequately addressed through labelling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
✓		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	8.1.1.
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

BV and trichomoniasis are common causes of vulvovaginitis especially among adolescent and young adult women. Clinical symptoms include vulvar pruritis, irritation and burning, and vaginal discharge (Agana *et al*., 2019). Factors including vaginal pH, the thickness of the vaginal mucosal layer, and the constituency of the microbiome that inhabits the vaginal wall impact susceptibility to vulvovaginitis.

2.1.1. Bacterial Vaginosis

BV is most often associated with an overgrowth of specific bacterial species, including *Gardnerella vaginalis*, Mobiluncus species, Bacteroides species, and a variety of other transient microflora, with a concomitant comparative decrease in Lactobacillus species (Ma *et al.*, 2012). In the United States, the National Health and Nutrition Examination Survey (NHANES) data estimates the prevalence of BV to be 29 percent in the general population of women aged 14 to 49 years and 50 percent in African-American women (Allsworth *et al*., 2007). Sexual activity is a risk factor for BV and the presence of other STIs appears to be associated with an increased prevalence of BV. Fifty to 75 percent of women with BV are asymptomatic. Symptomatic patients present with an off-white, thin, and homogeneous "fishy smelling" discharge. The diagnosis of BV is based on the presence of at least three of the following four Amsel criteria:

- Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls
- Vaginal pH greater than 4.5
- Positive whiff-amine test, defined as the presence of a fishy odor when 10 percent potassium hydroxide (KOH) is added to a sample of vaginal discharge
- Clue cells on saline wet mount, comprising at least 20 percent of epithelial cells

Gram stain of vaginal discharge is the gold standard for diagnosis of BV. The Gram-stained smear is evaluated using Nugent criteria (Nugent *et al*., 1991). The scoring system is summarized in Table 2-1. A Nugent score of at least 7 is indicative of BV. A score of 4-6 is considered intermediate and a score of 0-3 is considered normal.

Table 2-1. Nugent Scoring System for Gram Stain of Vaginal Smears

Lactobacillus **per field**	**Score**	***Gardnerella Bacteroides*** **per field**	**Score**	**Curved Gram variable rods per field**	**Score**
>30	0	0	0	0	0

5-30	1	<1	1	<1	1
1-4	2	1-4	2	1-4	2
< 1	3	5-30	3	5-30	3
0	4	>30	4	>30	4

Table produced by the reviewer based on Table 1 and contents of Nugent *et al*., 1991.
The numbers represent cells per high power oil immersion microscopic field.

There are epidemiological associations between BV and other adverse health outcomes, such as STIs including HIV, herpes simplex virus type 2 (HSV-2), gonorrhea, chlamydia, and trichomonas infections, postoperative infections, preterm birth, and other gynecological infections (Allworth *et al*., 2011). Women with symptomatic BV are generally treated with metronidazole, tinidazole, or clindamycin. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months.

2.1.2. Trichomoniasis

Trichomoniasis is an STI caused by a parasite, *Trichomonas vaginalis (TV*). In 2018, the estimated prevalence of trichomonas infections among people between 15 to 59 years of age was 2.6 million, with 470,000 in males and 2.1 million in females (Kreisel *et al.*, 2021). People aged 15 to 24 years comprise 15.6% of all prevalent infections. TV infection prevalence is disproportionately higher in black women, with 13% of individuals estimated to be infected as compared to 1.8% of white women (Sutton *et al.*, 2007). In sexually transmitted disease (STD) clinics, TV infection is reported to be present in 26% of symptomatic women and 6.5% of asymptomatic women (Meites *et al.*, 2013).

Many patients have minimal or no symptoms with TV infection, which may lead to a delay of treatment for months to years (Peterman *et al*., 2006; Sutton *et al*., 2007; Peterman *et al.*, 2009). More than 75% of males with TV infection were reported to have asymptomatic infection (Seña *et al.*, 2007) and when present, symptoms of urethritis, epididymitis, or prostatitis are likely to be transient and spontaneously resolve. Women with TV infection are more likely to be symptomatic over time and may experience symptoms ranging from purulent, malodorous vaginal discharge to urethritis, cystitis, and dyspareunia (Workowski *et al.*, 2021). Untreated disease in women is associated with adverse reproductive health consequences such as cervical neoplasia, pelvic inflammatory disease, and infertility (Grodstein *et al.*, 1993). Infected pregnant women are at increased risk of premature rupture of membranes, preterm birth, and delivery of low birthweight infants (Silver *et al.*, 2014). Infants born to infected mothers may become infected during delivery which may result in neonatal complications.

Trichomoniasis is easily transmitted between sexual partners during penile-vaginal intercourse. The rate of reinfection in patients treated for trichomoniasis is high (Peterman *et al.*, 2006). To avoid reinfection, partners are referred for presumptive therapy and advised to abstain from intercourse until they and their sexual partners have been adequately treated and symptoms have resolved. Also, retesting for TV is recommended for all sexually active women within 3 months following the initial treatment regardless of whether they believe their sexual partners were treated (Workowski *et al.*, 2021).

There are epidemiological associations between trichomoniasis and other adverse health outcomes, such as STIs including HIV infection (Kissinger *et al.,* 2013), gonorrhea, human papillomavirus (HPV) and HSV-2 infections, preterm birth, and other adverse pregnancy outcomes. Of note, TV infection in women with HIV is associated with increased risk of pelvic inflammatory disease (Moodley *et al.*, 2002).

In female patients who have a vaginal discharge, diagnostic testing for TV infection is typically performed. The diagnosis of trichomoniasis was classically established by microscopic evaluation of wet preparations of genital secretions where the organism can be directly visualized. When wet mount is negative, highly sensitive and specific laboratory tests including nucleic acid amplification tests (NAAT) and antigen-detection tests are available and should be used.

2.2. Analysis of Current Treatment Options

Table 2-2 summarizes the currently available treatments for BV. The CDC recommended therapies for BV include topical or oral metronidazole, topical or oral clindamycin, or oral tinidazole (Workowski *et al.*, 2021). There are no specific guidelines for adolescent patients. However, metronidazole vaginal gel 0.75% and 1.3%, and clindamycin vaginal suppositories are FDA approved for treatment of BV in pediatric patients.

Table 2-2. Currently Available Treatments for Bacterial Vaginosis

Recommended Regimens	Alternative Regimens	Additional Therapies[§]
Metronidazole 500 mg orally twice daily for seven days	Clindamycin 300 mg orally twice daily for seven days	Metronidazole gel 1.3% intravaginally as a single dose
Metronidazole 0.75% gel 5 g intravaginally once daily for five days	Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days	Clindamycin phosphate 2% vaginal cream in a single dose
Clindamycin 2% cream in 5g intravaginally once at bedtime for seven days	Secnidazole 2 g oral granules in a single dose	
	Tinidazole 2 g orally once daily for 2 days	
	Tinidazole 1 g orally once daily for 5 days	

§ Listed in CDC guidelines as additional therapies.
Table was made by the clinical reviewer based on CDC Sexually Transmitted Infectious Treatment Guidelines, 2021.

Table 2-3 summarizes the currently available treatment options for trichomoniasis. The CDC recommended therapies for trichomoniasis include oral tinidazole 2 gram as a single dose, oral metronidazole 2 gram single dose, or oral metronidazole 500 mg twice a day for 7 days. Notably, a recent randomized controlled trial showed that a 7-day course of metronidazole is more effective than a single dose (Kissinger *et al*., 2018). There are no specific guidelines and no drugs are approved for treatment of trichomoniasis in adolescent patients.

Table 2-3. Currently Available Treatments for Trichomoniasis

Recommended Regimen for Trichomoniasis in Women
Metronidazole 500 mg, 2 times/day for 7 days
Recommended Regimen for Trichomoniasis in Men
Metronidazole 2 g orally in a single dose
Alternative Regimen for Women and Men
Tinidazole 2 g orally in a single dose

Table was made by the clinical reviewer based on CDC Sexually Transmitted Infectious Treatment Guidelines, 2021.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original NDA 209363 for SOLOSEC (secnidazole) oral granules, 2 g, was approved on September 15, 2017, for treatment of bacterial vaginosis (BV) in adult women. On June 30, 2021, SOLOSEC was approved for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults. The approval of both indications included Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) for pediatric assessments in adolescent patients. Supplement 014 [PMR 3249-1] was submitted on March 29, 2021, and Supplement 016 [PMR 4113-1] on August 30, 2021, to expand the BV and trichomoniasis indications, respectively, to the adolescent population.

3.2. Summary of Presubmission/Submission Regulatory Activity

3.2.1. Bacterial Vaginosis

IND 117811 was submitted on December 18, 2013, for treatment of BV. The IND was granted qualified infectious disease product designation (QIDP) on November 18, 2014, and fast track designation on August 12, 2015, for this indication.

In a Type C clinical pharmacology meeting was held on January 21, 2015, wherein the Division recommended enrollment of adolescent postmenarchal females into the planned phase 3 studies of secnidazole. The initial Pediatric Study Plan (iPSP) was submitted on May 11, 2015. The Applicant requested a waiver for females younger than 12 years of age since the disease does not occur in this age group. The Applicant planned to enroll adolescent females ages 12 years or older in the pivotal BV study (SYM-1219-301) and in a safety study in BV patients (SYM-1219-350). A written response was sent on August 7, 2015, recommending a safety database of at least 40-50 postmenarchal pediatric subjects treated with secnidazole.

The revised iPSP for the treatment of BV was submitted on October 21, 2015, stating that the Applicant was not able to enroll any adolescent patients into the phase 3 pivotal BV study (SYM-1219-301) and only enrolled 2 adolescents in the safety study in BV patients (SYM-1219-350), primarily due to the requirement for parental consent for participation in the clinical trials. The Applicant proposed (b) (4) A written response was sent on November 6, 2015, stating that the Division did not agree with the proposed (b) (4) . The Division recommended the Applicant continue efforts to enroll 20-40 postmenarchal adolescent females with BV.

The Applicant submitted a revised iPSP on December 15, 2015. The Applicant proposed an open-label, safety study in 20-40 postmenarchal adolescent females with BV with deferral of the study until the approval of SOLOSEC for the treatment of BV in adults. On January 6, 2016, the Pediatric Review Committee (PeRC) concurred with the iPSP. The Division sent the agreed iPSP to the Applicant on January 14, 2016.

The NDA for SOLOSEC for the treatment of BV in adult patients was submitted on January 17, 2017, and a subsequent PeRC meeting was held on August 9, 2017. At this meeting PeRC concurred with granting the request for: (1) a full waiver in males and premenarchal adolescent females because studies are impossible or highly impractical, and (2) a deferral of a safety study in postmenarchal adolescent females ages 12 to less than 18 years of age with BV. With the approval of the NDA for treatment of BV in adults on September 15, 2017, the Applicant was issued PMR 3249-1 to "conduct an open label, multicenter, safety study of SOLOSEC (secnidazole) oral granules in healthy postmenarchal adolescent females ages 12 years to less than 18 years of age with bacterial vaginosis."

On December 13, 2017, a draft protocol was submitted for a safety study of SOLOSEC in adolescents with BV with a plan to enroll (b) (4) adolescent females. On March 6, 2018 and March 21, 2018, the Division recommended a sample size of at least 40 participants to have greater assurance of safety in adolescent females. The final protocol was submitted on March 28, 2018, to study the safety (and descriptive efficacy) of secnidazole in the treatment of 40 adolescent females with BV. The final data from this study (SYM-1219-401) are being reviewed in the current sNDA submission (S-014) to extend the BV treatment indication to adolescents.

On March 29, 2018, the Applicant submitted a Proposed Pediatric Study Request (PPSR) to study secnidazole for treatment of BV in pediatric patients. The Applicant proposed to only study pediatric patients with BV which is consistent with the PREA requirements but did not include other potential indications that secnidazole has been approved for outside of the U.S. On June 13, 2018, PeRC determined that additional indications will need to be added to the Written Request (WR). An inadequate study request letter was sent on June 14, 2018, wherein the Division found the PPSR inadequate and a WR could not be issued.

On August 15, 2018, a PeRC meeting was held to discuss the deferral extension request for PMR 3249-1 to delay the start of the safety study of adolescents with BV for 12 months. PeRC agreed with the Division's recommendation to deny the deferral extension request, citing inadequate justification for delaying the PMR.

The Applicant submitted Supplement 014, on March 29, 2021. The submission provides for the final study report for PMR 3249-1, and a request to add adolescent females 12 years of age and older to the approved indication of treatment of BV. The supplement has a PDUFA goal date of January 29, 2022.

3.2.2. Trichomoniasis

On December 18, 2018, a type C meeting was held to discuss the development plan of secnidazole for the treatment of trichomoniasis. The Applicant stated that they had challenges with designing a study to include males, but the Division recommended that the Applicant make a reasonable attempt to enroll males.

On July 11, 2019, the Applicant submitted an iPSP for the treatment of trichomoniasis and an agreed iPSP was established on October 8, 2019. The Applicant requested a waiver for females and males younger than age 12 years since the disease does not occur in this age group. The Applicant also requested a waiver for adolescent males aged 12 years to less than 18 years of age, since the infection is generally asymptomatic in men and it is very difficult to identify males for participation in a study that are not partners of infected female patients. The Applicant noted that the clinical safety and efficacy would be evaluated in adolescent and adult females with trichomoniasis in the planned phase 3 study (SEC-WH-301).

On February 14, 2020, the Applicant notified the Division of challenges with the recruitment of adolescents for the phase 3 study of trichomoniasis treatment (SEC-WH-301) and the post-market PREA study in adolescent females with BV (SYM-1219-401). A teleconference was held on March 2, 2020. The Applicant explained that pediatric enrollment was minimal, while the overall enrollment goal had been met for the trichomoniasis study. The Applicant stated that they planned to reference the study of SOLOSEC in adolescents with BV (SYM-1219-401) to support the safety of SOLOSEC for treatment of trichomoniasis in adolescent females. The Division agreed to this on March 27, 2020. Regarding the BV study, the Applicant asked if (b) (4) adolescent females would be sufficient. The Division recommended continuing enrollment in the BV study with a goal of meeting the planned target of 40 subjects.

A supplemental NDA for the treatment of trichomoniasis in adult patients was submitted on August 31, 2020. A PeRC meeting was held on May 4, 2021, to discuss the trichomoniasis treatment indication. PeRC agreed to granting a partial waiver for males and females from birth to <12 years of age. The PeRC concluded that the safety data provided for BV by the adolescent safety study (SYM-1219-401) may be considered for the safety assessment of the trichomoniasis treatment indication in females 12 years and older. PeRC agreed with the Division that the trichomoniasis treatment indication in males 12 years and older would be justified based on the adult male data presented in the original trichomoniasis supplemental NDA and safety data from study SYM-1219-401. They also determined that the PREA PMR for BV may be considered fulfilled by study SYM-1219-401. PeRC recommended that the Division note in the approval letter for the trichomoniasis treatment indication in adults that pediatric safety data for the BV treatment indication had already been submitted and was under review. Additionally, PeRC recommended that the Division issue a PREA PMR for a pediatric assessment for the trichomoniasis treatment indication. With the approval of the sNDA for treatment of trichomoniasis for adult patients on June 30, 2021, PMR 4113-1 was issued for a pediatric assessment of SOLOSEC for treatment of trichomoniasis in adolescent females and males aged

12 years to less than 18 years.

The Applicant submitted Supplement 016, on August 30, 2021. The submission provides for the final study report for PMR 4113-1, and a request to add patients 12 years of age and older to the approved indication of treatment of treatment of trichomoniasis caused by TV. The supplement has a PDUFA goal date of June 30, 2022.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The sNDA submissions contained data from a single open-label safety study; no OSI inspections were conducted.

4.2. Product Quality

SOLOSEC is a marketed drug. There were no proposed changes to the current chemistry, manufacturing, or controls.

4.3. Clinical Microbiology

No new clinical microbiology studies were included in the two NDA supplements. A comprehensive assessment of the Clinical Microbiology information for secnidazole was provided in the original NDA for the treatment of bacterial vaginosis in adult women, as well as, the sNDA (S-012) for treatment of trichomoniasis in adults and reviewed previously (for details see the clinical microbiology review dated August 8, 2017, and Section 4.3 of the unireview dated June 30, 2021, respectively).

From the clinical microbiology perspective, no changes are recommended in the current approved labeling.

5 Nonclinical Pharmacology/Toxicology

There were no nonclinical pharmacology or toxicology data submitted. The reader is referred to Dr. Owen McMaster's review of the pharmacology/toxicology data in the original NDA submission.

6 Clinical Pharmacology

6.1. Executive Summary

No clinical pharmacology studies are included in these sNDAs. A comprehensive assessment of the Clinical Pharmacology program for SOLOSEC was provided in the original NDA.

6.2. Summary of Clinical Pharmacology Assessment

The SOLOSEC dose proposed for the treatment of BV in adolescent females and the treatment of trichomoniasis in adolescents is a single 2-gram packet of granules taken orally. This is the same dose and formulation approved for the adult BV and trichomoniasis patient populations. A comprehensive assessment of clinical dose response was provided in the original marketing application (study SYM-1219-201). While no pediatric PK data were submitted with the NDA, the PK profile of secnidazole in adolescent patients is anticipated to be similar to that in adults. The dose is appropriate for the treatment of BV and trichomoniasis in adolescents given the similarities in physiology and disease progression between adolescent and adult patients for both indications.

The rationale for extrapolating efficacy from the adult BV and trichomoniasis patient populations and safety from the adolescent BV patient population is acceptable from a Clinical Pharmacology perspective (See Section 7 for more details). We do not recommend any changes to the proposed labeling in the relevant Clinical Pharmacology sections.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Clinical studies relevant to these efficacy supplements are listed in Table 7-1.

Table 7-1. Listing of Clinical Studies Relevant to this NDA/BLA

Study Identity	NCT no.	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Uncontrolled Study to Support Safety								
SYM-1219-401	03937869	Phase 4, multi-center, open-label for the treatment of BV	Granules, 2 grams single dose, oral, sprinkled on applesauce	Primary safety endpoints: Adverse events (AEs), Vital signs, Physical examination, Pelvic examinations, Laboratory assessments Secondary efficacy endpoints: Clinical outcome at TOC (Day 7-14), Nugent score outcome at TOC, Investigator's clinical assessment at TOC, Subject's continued clinical response at Day 21-30.	Single dose/days 21-30	40	Non-pregnant adolescent females 12-17 years of age with BV	6 centers in the U.S.
Controlled Studies to Support Efficacy and Safety								
SYM-1219-201	02147899	Phase 2, multi-center, parallel groups, placebo-, controlled, double blind trial for the treatment of BV	Granules, 1 gram or 2 grams single dose, oral, sprinkled on applesauce	The primary endpoint was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). A Clinical Outcome Responder was defined as a patient with all of the following: 1) Normal vaginal discharge 2) Negative 10% KOH Whiff test	Single dose/ days 21-30	Total: 215 SOLOSEC 2 g: 72 SOLOSEC 1 g: 71	Women at least 18 years of age with BV	24 centers in the U.S.

				3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline. The following secondary endpoints were evaluated at the TOC/EOS visit (Day 21 to 30): Nugent Score; Therapeutic Outcome (Clinical Outcome Responder plus normal Nugent score). Safety endpoints: Adverse events (AEs), Vital signs, Physical examination, Pelvic examinations, Laboratory assessments		Placebo: 72		
SYM-1219-301	0241 8845	Phase 3, multi-center, parallel groups, placebo-controlled, double-blind trial for the treatment of BV	Granules, 2 grams single dose, oral, sprinkled on applesauce	The primary endpoint was similar to study SYM 1219-201 which was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). The following secondary endpoints were evaluated at the Interim visit (Study Day 7-14) and the TOC/EOS visit (Study Day 21 to 30): Nugent Score, Therapeutic Outcome (Clinical Outcome Responder with a normal Nugent score), Clinical Outcome (Interim Visit only), Investigator's Clinical Assessment (Investigator's opinion of the need for additional BV treatment at the TOC/EOS Visit only). Safety endpoints: Adverse events (AEs), Vital signs,	Single dose/ days 21-30	Total: 189 SOLOSEC 2g: 125 Placebo: 64	Women and post-menarchal adolescent girls with BV	21 centers in the U.S.

				Physical examination, Pelvic examinations, Laboratory assessments				
SEC-WH-301	0393 5217	Phase 3, multicenter, randomized, double-blind, placebo-controlled, delayed treatment trial for TV	SOLOSEC: 2-gram single oral dose Placebo: After test of cure (TOC) visit (Day 6-12), treatment was switched.	Microbiological cure (a negative TV culture) at TOC visit	Once/TOC and one follow-up visit (7-12 days post TOC)	Total: 147 SOLOSEC 2g: 74 Placebo: 73	Adult females or post-menarchal adolescent girls ≥ 12 years of age, with positive TV culture and negative results for other STIs	10 centers in the United States
Other studies pertinent to the review of efficacy or safety in males								
SYM-1219-104		Phase 1, randomized, placebo-controlled, single-blind, two part study	Granules, 4 or 6 grams single dose, oral, sprinkled on applesauce	Assess PK and safety	Single dose	Part A: 8 Part B: 8 Female: 8 Male: 8	Healthy adult females and males	Single Center in U.S.
SYM-1219-105		Phase 1, double-blind, randomized, placebo-controlled, 4-period, single-dose, crossover trial	Granules, 2 or 6 grams single dose, oral, sprinkled on applesauce, placebo, moxifloxacin	QT/QTC Study	Single dose	Total: 52 Female: 22 Male: 30	Healthy adult females and males	Single Center in U.S.

7.2. Review Strategy

In this review of pediatric efficacy supplements for SOLOSEC, there are two indications evaluated: treatment of bacterial vaginosis in adolescent females (S-014) and treatment of trichomoniasis caused by TV in adolescents (S-016). Review of each indication will be described separately. As both efficacy supplements are supported by the same study SYM-1219-401, the decision was made to combine the review of the supplements and take action on both sNDAs at the same time.

7.2.1. Treatment of Bacterial Vaginosis

Evidence for the safety of SOLOSEC in adolescent females with BV is based on a multi-center, open-label study which enrolled 40 females 12 to less than 18 years of age with BV to receive a single dose of SOLOSEC 2g oral granules (SYM-1219-401). The safety section of this review will focus on data from study SYM-1219-401. Evidence for the efficacy of SOLOSEC for treatment of BV in adolescent females was primarily based on extrapolation of data from controlled trials conducted in adult females (SYM-1219-201 and SYM-1219-301) which were reviewed in the original NDA. The SYM-1219-401 safety study in adolescents with BV had secondary efficacy endpoints which provided supportive data regarding the efficacy of SOLOSEC. The efficacy review section will focus on the data related to the secondary efficacy endpoints from study SYM-1219-401.

7.2.2. Treatment of Trichomoniasis

Evidence for the safety of SOLOSEC in adolescent females with trichomoniasis is based on the safety data from the SYM-1219-401 study in female adolescents with BV. The evidence for the safety of SOLOSEC in adolescent males includes safety data from study SYM-1219-401, phase 1 studies of SOLOSEC in healthy male volunteers (SYM-1219-104 and SYM-1219-105), and published studies evaluating secnidazole for the treatment of trichomoniasis in males. Evidence for the efficacy of SOLOSEC for treatment of trichomoniasis in adolescent females is based on extrapolation of data from a controlled trial conducted in adult females (SEC-WH-301), which was reviewed in a prior efficacy supplement (S-012). Evidence for the efficacy of SOLOSEC for treatment of trichomoniasis in adolescent males is based on extrapolation of efficacy data from the controlled trial conducted in adult females (SEC-WH-301) with supportive data from published reports of studies conducted to evaluate secnidazole for the treatment of trichomoniasis in adolescent and adult males.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study SYM-1219-401

Study Design

Study SYM-1219-401 was an open-label, non-comparative, multicenter study designed to assess the safety of a single dose of SOLOSEC (secnidazole) 2 g oral granules for the treatment of BV in adolescent girls. Assessment of efficacy including clinical response and microbiological response was a secondary objective. The study was to be conducted at 11 research centers in the United States; however, only 6 of the 11 centers enrolled subjects. The first subject was enrolled on November 28, 2018, and the last subject completed the study on November 5, 2020.

Eligible subjects included adolescent girls 12 to less than 18 years of age with a clinical diagnosis of BV defined as having an off-white (milky or gray), thin, homogeneous vaginal discharge; a vaginal pH > 4.5; presence of clue cells ≥ 20% of the total epithelial cells on microscopic examination of the vaginal saline wet mount; and a positive 10% KOH whiff test. Subjects were not eligible if they were suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including candidiasis, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae* or herpes simplex or human papilloma virus; had active genital lesions, including active herpes simplex lesions, or other vaginal or vulvar conditions which could confound the interpretation of the clinical response, as determined by the investigator (subjects with genital warts that were not being treated could be enrolled); or had received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days prior to the Baseline Visit (Day 1).

All subjects received a single oral dose of SOLOSEC (secnidazole) 2 g granules on Day 1; the dose that is approved for the treatment of BV in adult women. The study medication was mixed with 4 ounces of unsweetened applesauce and administered by the study subject, without regard to meals. After taking the dose of study medication, the subject was instructed to drink approximately 8 ounces of water. The treatment kits included Mott's® applesauce, a spoon, and an 8 ounce bottle of water.

Subjects returned to the study site once between Day 7-14 for a test of cure (TOC) visit. A follow-up telephone call was made at Days 21-30 to assess continued clinical response to treatment and adverse events.

Study Endpoints

The primary objective of the study was to assess the safety of SOLOSEC when used to treat adolescent girls with BV. Therefore, all efficacy evaluations were considered secondary endpoints.

Efficacy endpoints included:

- Clinical outcome at TOC: A Clinical Outcome Responder was defined as a subject with resolution of abnormal discharge, negative 10% KOH Whiff test, and clue cells < 20%.
- Nugent outcome at TOC: A score of 0-3 was considered normal and a score ≥ 4 was considered abnormal.
- Investigator's Clinical Assessment at TOC: Investigator's opinion of the need for additional BV treatment (Yes or No).
- Subject's Continued Clinical Response at Day 21-30: Investigator's opinion of continued clinical response to treatment (Yes or No).

Reviewer's Comment: *The definition of Clinical Outcome Responder is the same as that used in the adult BV studies conducted for SOLOSEC and is consistent with the definition of the primary endpoint of Clinical Cure recommended in the 2019 Bacterial Vaginosis: Developing Drugs for Treatment Guidance for Industry (also referred to as the 2019 BV guidance in this review)[1]. The primary timepoint of assessment for clinical outcome used in the adult studies for SOLOSEC was Day 21-30 rather than Day 7-14 but clinical outcome was also assessed at Day 7-14 in the phase 3 adult study. Since the primary objective of this study was for safety, it was agreed during the design of the study that an in-clinic visit at Day 21-30 would not be necessary. It should also be noted that the 2019 BV guidance suggests that the primary timepoint for assessment of efficacy for a systemic drug administered for 1 day and with a half-life shorter than 24 hours, such as SOLOSEC, could be the Day 7-14 visit. All of the SOLOSEC studies were conducted and/or started prior to the release of the 2019 BV guidance.*

Safety was evaluated through assessment of adverse events, vital signs (blood pressure, temperature and pulse), physical examinations, pelvic examinations (external genitalia and vagina), and laboratory assessments (hematology, serum chemistry, and urinalysis).

Statistical Analysis Plan

The statistical analysis plan (SAP) was finalized on March 22, 2019 and implemented prior to database lock. Although the SAP was finalized after study start, there were no changes in the SAP compared to the statistical details provided in the protocol specified prior to study start.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bacterial-vaginosis-developing-drugs-treatment-guidance-industry

Analysis Populations

The safety population consists of all enrolled subjects who received study medication. The safety population is used for all safety analyses.

The intent-to-treat (ITT) population included all enrolled subjects.

The modified intent-to-treat (mITT) population includes all enrolled subjects who met all inclusion/exclusion criteria. Efficacy analyses were conducted on the mITT population.

Reviewers' Comment: *The mITT definition currently used in BV trials only excludes subjects if they subsequently demonstrate a positive test result for other concomitant vaginal or cervical infections at baseline or have a baseline Nugent score less than 7 (the previous BV guidance recommended a cutoff of Nugent score less than 4 and this is what was used in the adult SOLOSEC studies). These are acceptable reasons for exclusion from an mITT population since they are based on data collected at baseline but whose results are not known until after treatment and the presence of concomitant STIs may interfere with the assessment of BV efficacy. Although the protocol definition of the mITT population states subjects would be excluded if they did not meet all of the inclusion/exclusion criteria, the only reason for exclusion from the mITT population in this study was due to not having a negative STI result (see below under Patient Disposition) which is acceptable.*

Analysis Methods

No hypothesis testing was conducted. The efficacy results of the study are summarized descriptively with the number and percentage of subjects for each endpoint. Subjects with any missing data at TOC due to treatment failure or early discontinuation were imputed as a non-responder for the clinical outcome. No other imputation was done.

Sample Size Calculation

The sample size chosen for the study was not based on statistical considerations. A sample size of approximately 40 subjects was chosen to provide observational safety data only.

Interim Analysis

No interim analysis was planned or conducted.

Protocol Amendments

The original protocol was dated March 23, 2018. One amendment dated August 27, 2019, was implemented. The primary reason for the amendment was to remove the need for parental consent for participation in the study. This modification to the protocol did not have an impact on the integrity of the trial or the interpretation of the results.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in the compliance with Good Clinical Practices (GCPs) including independent quality assurance and archiving of essential documents.

Financial Disclosure

No clinical investigators other than Dr. (b) (6) (Principal Investigator for Site (b) (6) that enrolled (b) (6) subjects in study SYM-1219-401) had any disclosable interests of financial arrangements. Dr. (b) (6) submitted a financial disclosure form, explaining that he received compensation for speaker bureaus training, lectures, marketing commercial, and a consulting fee. In response to an information request, on December 22, 2021, the Applicant submitted the following explanation regarding steps taken to minimize the potential bias in study SYM1219-401:

- This was an open label multi-center study with specific inclusion/exclusion criteria and where all patients received the same single dose of test product.
- One of the efficacy endpoints for the study was based on Nugent Score results that were analyzed and results reported by an independent central laboratory.
- The study was monitored by an independent Clinical Research Associate who is trained to identify and report potential of bias and/or fraud, during routine monitoring visits.
- Statistical analysis for the study was performed by an independent statistician, who was responsible for analyzing study endpoints and assessment of study outcome.
- None of the payments to Dr. (b) (6) were made to fund ongoing research or laboratory activities or equipment.

Patient Disposition

A total of 40 subjects were enrolled in the study. All enrolled subjects received treatment. Therefore, the ITT and Safety populations are the same. Four subjects did not have a negative STI test result at baseline and were excluded from the mITT population. Therefore, the mITT population includes 36 subjects.

Table 8-1: Analysis Populations

Analysis Population	SOLOSEC N (%)
Enrolled	40 (100)
Safety	40 (100)
ITT	40 (100)
mITT	36 (90)

All subjects enrolled took the single dose of treatment and therefore completed treatment. Overall, 37 (92.5%) subjects completed the study. Three subjects discontinued the study early. All 3 were discontinued due to a positive STI test result at baseline.

Table 8-2: Subject Disposition

	SOLOSEC N (%)
Enrolled	40 (100)
Completed Treatment	40 (100)
Discontinued Treatment	0 (0)
Completed Study	37 (92.5)
Discontinued Study	3 (7.5)
Positive for STI at Baseline	3 (7.5)

Source: Table 5 of Clinical Study Report

Protocol Violations/Deviations

No major protocol deviations were reported. Commonly reported minor protocol deviations included errors in the informed consent process (3 subjects), out-of-window visits (7 subjects), use of prohibited medications (1 subject), and study procedures (15 subjects).

Demographic and Other Baseline Characteristics

The following table summarizes demographic and baseline characteristics of subjects in the Safety population. All subjects were female. The mean age was 15.3 years with a range of 12 to 17 years. Most subjects were White (60%) or Black (37.5%). The median number of BV episodes reported in the past 12 months (including the current episode) was 2 episodes. The mean Nugent score at baseline was 6.1.

Table 8-3: Demographic and Baseline Characteristics (Safety population)

Parameter	**SOLOSEC** (N=40)
Sex	
Female	40 (100%)
Race	
White	24 (60.0%))
Black	15 (37.5%)
Other	1 (2.5%)
Age (years)	
Mean (sd)	15.3 (1.6)
Median	16

Min, Max	12, 17
Number of BV episodes in the past 12 months	
Mean (sd)	2.5 (2.3)
Median	2
Min, Max	1, 11
1-2	28 (70%)
>2	12 (30%)
Nugent Score	
Mean (sd)	6.1 (3.1)
Median	7
Min, Max	0, 10
0-3	10 (25%)
4-6	7 (17.5%)
7-10	23 (57.5%)

Source: Reviewer conducted analysis using ADSL dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 40 subjects received study drug and took the full dose of study medication within 5 minutes of administration.

Overall, 17 of 40 (42.5%) subjects used at least 1 concomitant medication. The most commonly used concomitant medications were systemic hormonal contraceptives (7/40 subjects), metronidazole (4/40 subjects), and iron preparations (3/40 subjects). Three of the 4 subjects who received metronidazole received it at the TOC visit due to treatment failure. The fourth subject who received metronidazole received it starting on Study Day 40.

Efficacy Results

The following table summarizes the efficacy assessments for the mITT population. At the TOC visit on Day 7-14, the clinical responder rate was 77.8% (28/36) and 38.9% (14/36) of subjects had a normal Nugent score (i.e., 0 to 3). In the Investigator's opinion, 3 subjects (8.3%) needed additional BV treatment at the TOC visit. A continued clinical response was reported by the Investigator in 28 of 34 subjects who were contacted with the follow-up telephone call between Day 21-30.

Table 8-4: Efficacy Assessments (mITT population)

Parameter	**SOLOSEC** (N=36)	
	n (%)	Exact 95% CI
Clinical Responder at TOC		
Yes	28 (77.8)	(60.9, 89.9)
No	8 (22.2)	
Nugent Score at TOC		

Normal	14 (38.9)	(23.1, 56.5)
Abnormal	22 (61.1)	
Need for Additional BV treatment at TOC		
Yes	3 (8.3)	(1.8, 22.5)
No	33 (91.7)	
Continued Clinical Response at follow-up		
Yes	28 (77.8)	(60.9, 89.9
No	6 (16.7)	
Unknown	2 (5.5)	

Note: TOC visit was Day 7-14 and follow-up telephone call was Day 21-30.
Source: Reviewer conducted analysis using ADEFF dataset

Clinical responder rates at TOC by various subgroups are summarized in the following table for the mITT population. Interpretation of these results must be made with caution given the limited sample sizes. However, the clinical responder rates were consistent across the various subgroups with those seen for the overall population.

Table 8-5: Clinical Responder at TOC (Day 7-14) for Various Subgroups (mITT population)

Subgroup	**SOLOSEC** n/N (%)
Race	
White	17/21 (81.0)
Black	10/14 (71.4)
Other	1/1 (100)
Baseline Nugent Score	
0-3	7/10 (70.0)
4-6	6/7 (85.7)
7-10	15/19 (79.0)
Number of prior episodes of BV in past 12 months	
1-2	20/26 (76.9)
>2	8/10 (80.0)

Source: Reviewer conducted analyses using ADEFF and ADSL datasets

8.1.3. Integrated Assessment of Effectiveness

8.1.3.1. Bacterial vaginosis

Determination of the effectiveness of SOLOSEC in the treatment of BV in adolescent females aged from 12 years to less than 18 years was primarily based on extrapolation of the efficacy data from controlled trials in adult females [SYM-1219-201 (Phase 2) and SYM-1219-301 (Phase 3)], which were reviewed in the original NDA. Clinical outcome was evaluated at the TOC/EOS visit (Day 21 to 30) in the mITT population. In study SYM 1219-201, the clinical outcome responder rates were 67.7% (42/62) in the 2 gm secnidazole arm compared to 17.7% (11/62) in the placebo arm ($p<0.001$). In study SYM 1219-301, the clinical outcome responder rates were 53.3% (57/107) in the 2 gm secnidazole arm compared to 19.3% (11/57) in the placebo arm ($p<0.001$). The similarity of the pathophysiology of BV in adolescents and adults and the

expectation that the pharmacokinetics of the single 2 g SOLOSEC dose in adolescents is similar to adults support the extrapolation of efficacy data from trials of SOLOSEC in treatment of BV in adults.

The efficacy supplement (S-014) for the treatment of BV in adolescents contains data from a single non-comparative study (SYM-1219-401) that was conducted to provide supportive information regarding the efficacy of SOLOSEC in adolescent females for the treatment of BV. Overall, the results observed in SYM-1219-401 in adolescents were favorable and generally consistent with those observed in the adult SOLOSEC phase 3 BV study, SYM-1219-301. The clinical responder rates and normal Nugent Score rates at Day 7-14 for SOLOSEC in Studies SYM-1219-401 and SYM-1219-301 are presented in the following table.

Table 8-6: Efficacy Assessments for SOLOSEC in Adolescent and Adult Females

Assessment	Adolescent Study SYM-1219-401		Adult Study SYM-1219-301
	mITT population (n=36)	Subset of mITT with baseline Nugent score ≥4 (n=26)	mITT population (n=107)
Clinical Responder at Day 7-14	28 (77.8)	21 (80.8)	62 (57.9)
Nugent score Normal at Day 7-14	14 (38.9)	6 (23.1)	49 (45.8)

Note: The mITT population for the adult study excluded subjects with a Nugent score <4 in addition to those with a positive STI test result at baseline. Therefore, for the adolescent study, the subset of the mITT population with a baseline Nugent score ≥4 is most consistent with the mITT population of the adult study.
Source: Adapted from Table 8-4 and Table 8-5 of this review and Table 5 of the current SOLOSEC prescribing information

8.1.3.2. Trichomoniasis

Determination of the effectiveness of SOLOSEC for the treatment of trichomoniasis in adolescents aged 12 years to less than 18 years was primarily based on extrapolation from the data from an adequate and well-controlled clinical study in adult females (SEC-WH-301) which was reviewed in efficacy supplement S-012. A single 2 g dose of SOLOSEC was shown to be superior to placebo in terms of microbiological cure at 6-12 days after treatment with a treatment difference of 90.7% and a 95% confidence interval of 80.7%, 96.5%. Additionally, microbiological cure with symptom resolution at TOC was also significantly higher in the SOLOSEC group compared to the placebo. The pathogenesis of trichomoniasis in adolescents is the same as that in adults which supports the extrapolation of efficacy data from controlled trials of SOLOSEC for treatment of trichomoniasis in adults.

Since trichomoniasis is a less severe disease in males than females and is often self-limited, the efficacy of SOLOSEC for treatment of trichomoniasis in males was extrapolated from the data obtained from controlled trichomoniasis trials in females, along with supporting evidence from the published studies evaluating secnidazole for treatment of trichomoniasis in males. A single oral 2 g secnidazole dose was assessed in four open-label studies in males (Dyudyun *et al*., 2016; Özbilgin *et al*, 1994; Siboulet *et al.*, 1977; Videau *et al.*, 1978) that reported cure rates ranging from 91.7% (165/180) to 100% (30/30) at time points ranging from 2 to 20 days (n=437, 211 males and 226 females). The studies are summarized in Table 8-7, below.

Table 8-7. Published Clinical Studies of Secnidazole for Treatment of Trichomoniasis in Males

Publication (Country)	Treatment(s)	Study Design	Demographics		Clinical Endpoint(s)
			M / F	Age Range	
Actively Controlled					
Özbilgin *et al*., 1994 (Turkey)	Secnidazole, 2 g SD, PO	Open label, comparative study of SD secnidazole, MD metronidazole, and MD ornidazole	30 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
	Metronidazole, 250 mg TID × 7 days, PO		29 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
	Ornidazole, 500 g BID × 5 days, PO		26 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
Uncontrolled					
Videau *et al*., 1978 (France)	Secnidazole, 2 g SD, PO	Open label, SD, uncontrolled study	56 /84	**15 – 54[§]**	Cure rate at 48 hours (97.1%) Day 15 relapse/reinfection rate (4.4%)
Siboulet *et al*., 1977 (France)	Secnidazole, 2 g SD, PO	Open label, SD, uncontrolled study	76 /104	**12 – 54[§]**	Clinical symptom score: Men (N=63): Very good (60.3%), Good (20.6%), Average (15.9%), Failure (3.2%) Women (N=87): Very good (62.1%), Good (23.0%), Average (9.2%), Failure (5.7%) Microbiological cure rate: • Immediate, 2-3 days after treatment (95.6%) • Long-term, 5-20 days after treatment (91.7%)
Dyudyun *et al*., 2016 (Ukraine)	Secnidazole, 2 g SD, PO ("fresh" trichomoniasis[b]) Or Secnidazole, 2 g given on Day 1, 3, and 5 (chronic trichomoniasis)	Open label, SD or MD, uncontrolled study	49 /38	18 - 57	Clinical and microbiological cure rate (97.7%)

BID=twice daily; F=female; M=male; MD=multiple dose; NR=not reported; PO=by mouth; SD=single dose, TID=three times daily.

[§] Study Population with Adolescents

[a] Age range for study population (n=415) is 18-50 years.

[b] Article originally published in Ukrainian. "Fresh" is interpreted to mean a patient with first occurrence of TV infection.

Source: Adapted from Applicant's supporting document, "efficacy-men-082820.pdf" (s-012, Module 5.4, Table 2.2) and modified by the Reviewer.

Clinical Reviewer Comment:

The Applicant did not recruit male subjects in the adult trichomoniasis study (SEC-WH-301) because males are typically asymptomatic and have higher spontaneous cure rates which could

affect the study endpoints and sample size. The evidence to support the use of secnidazole for treatment of trichomoniasis in males is provided by four open-label studies in the published literature. These studies were reviewed in the previous efficacy sNDA (S-012). Of the four open-label studies reviewed, two uncontrolled studies, Videau et al. and Siboulet et al., included adolescents aged 15 years and older and 12 years and older, respectively. However, there was no detailed description regarding how many adolescent males were in these studies. All four studies showed a response rate of greater than 90% at all timepoints for parasitological and clinical response which is consistent with the findings in the adult female study SEC-WH-301 and supportive of a treatment effect in both adult and adolescent males. Even though these studies were not conducted in the U.S., the pathogenesis and pathophysiology of BV and trichomoniasis are expected to be similar in people living in other countries, these results can be applied to patients in the U.S.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of SOLOSEC was previously reviewed in the original NDA for the BV treatment indication and the sNDA (S-012) for the trichomoniasis treatment indication. The current safety review primarily focuses on the safety findings from the phase 4 study (SYM-1219-401) conducted to support the proposed indications for treatment of BV in adolescent females and treatment of trichomoniasis in adolescent females and males.

Safety analyses were performed using datasets submitted by the Applicant with JMP version 15.0 analytical software.

Where relevant, data are compared to the original NDA (treatment of BV in adult women) and sNDA S-012 (treatment of trichomoniasis in adults), in which the safety population also received a single dose of 2 g SOLOSEC.

8.2.2. Review of the Safety Database

Overall Exposure

In study SYM-1219-401, 40 subjects were exposed to a single 2 g of SOLOSEC.

Adequacy of the safety database:

Overall, the safety database provided an adequate number of exposed adolescent subjects at the proposed dose (2 g) and frequency (one-time use) for the BV treatment indication. It should be noted that the prevalence of BV is about 50% in Black or African American women, and in study SYM-1219-401, 37.5% of the patients were Black or African American.

These data augment the safety information provided in the original NDA and sNDA S-012, in which a total of 592 subjects were exposed to a single 2 g SOLOSEC dose across four studies: three studies submitted to support the BV treatment indication (197 subjects in two controlled studies and 321 in one open label safety study) and one controlled study submitted to support the trichomoniasis indication (74 subjects).

The sNDA S-012 for the treatment of trichomoniasis included published studies of secnidazole for the treatment of males with trichomoniasis which were used as supportive evidence demonstrating the efficacy of SOLOSEC in this population (see section 8.1.4). These data are also used to support the safety of SOLOSEC for treatment of adolescent males with trichomoniasis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Case report forms were reviewed to assess the consistency of the data submitted. The reported terms for Adverse Events (AEs) matched the MedDRA dictionary terms used during the study.

Categorization of Adverse Events

The severity of the AEs were characterized as:

- **Mild**: AE which is easily tolerated
- **Moderate**: AE sufficiently discomforting to interfere with daily activity
- **Severe**: AE which prevents normal daily activities

When the intensity of an adverse event changed more than once a day, the maximum severity for the event was listed. If the intensity changed over a number of days, these mini-events or changes were recorded separately (i.e., having distinct onset dates).

Clinical Reviewer Comment: *The Applicant's categorization of AEs was acceptable.*

Routine Clinical Tests

A schedule of study procedures is provided in Table 8-8. The timing of clinical assessments in the safety population is adequate.

Table 8-8: Schedule of Assessments

Assessment	Baseline Visit	Test of Cure (TOC) / EOS Assessment	Subject Telephone Interview
	Day 1	Day 7-14	Day 21-30
Informed consent/assent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X	X	
Height/weight	X		
Urine pregnancy test[1]	X	X	
Physical examination	X	X[5]	
Pelvic examination	X	X	
External genitalia and vaginal exam	X	X	
Vaginal discharge assessment	X	X	
Vaginal wet mount for Clue cell assessment	X	X	
Gram stain of vaginal fluid	X[2]	X	
10% KOH Whiff test	X	X	
pH of vaginal fluid	X		
STI Assessments	X	X[3]	
OSOM® Trichomonas Rapid Test	X[4]		
Bimanual pelvic examination	X	X[6]	
Labs: Hematology, chemistry, and urinalysis	X[2]	X	
Drug dosing	X		
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Telephone interview of subject			X
Investigator's Clinical Assessment		X	

1. Performed by site personnel (not sent to central laboratory).
2. Results were not available at the time of enrollment.
3. Only as indicated as determined by the Investigator.
4. It was recommended that the vaginal sample for the OSOM® Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation.
5. A targeted physical examination at the TOC/EOS Visit was only needed per the Investigator's discretion if a reported AE required further evaluation.
6. A bimanual pelvic examination was required for all subjects at Baseline and was performed after the vaginal discharge assessment and all vaginal samples were collected. At the Investigator's discretion, a bimanual pelvic examination was performed at the TOC/EOS Assessment after the vaginal discharge assessment and all of the vaginal samples were collected.

Table obtained from page 22 of the Complete Study Report of SYM-1219-401

8.2.4. Safety Results

Deaths

No deaths were reported in the study.

Serious Adverse Events

There were no SAEs reported in the study.

Dropouts and/or Discontinuations Due to Adverse Effects

No subject in study SYM-1219-401 discontinued study treatment.

Significant Adverse Events

No other significant adverse events were reported in the study.

Treatment Emergent Adverse Events and Adverse Reactions

Four TEAEs occurred in three patients (3/40, 7.5%). Two TEAEs were related to the treatment; both occurred in a single patient. These treatment-related TEAEs were nausea and upper abdominal pain which were among the most common adverse reactions reported in the BV treatment studies in adult female patients.

Table 8-9: Summary of Treatment Emergent Adverse Events in Study SYM-1219-401 (Safety Population)

System Organ Class Preferred Term	Total N=40
Any TEAE	
Overall	3 (7.5%)
Gastrointestinal Disorders	
Overall	2 (5.0%)
Abdominal pain upper	1 (2.5%)
Nausea	1 (2.5%)
Toothache	1 (2.5%)
Infections and Infestations	
Overall	1 (2.5%)
Bacterial vaginosis	1 (2.5%)

Source: Clinical reviewer generated, SYM-1219-401 ADAE dataset

Laboratory Findings

Sporadic abnormal laboratory values were observed, but no clinically significant abnormal values or trends were observed. No clinically significant changes of overall mean, median, or min/max changes from baseline in any laboratory parameter were observed.

Vital Signs

No clinically significant abnormal findings were observed with blood pressure, pulse, temperature, and height/weight results, and none were reported as adverse events.

Electrocardiograms (ECGs)

Electrocardiograms were not performed in study SYM-1219-401. According to the original NDA review, the *in vitro* cardiac toxicity studies and safety ECGs in the clinical pharmacology studies did not show significant ECG abnormalities.

QT

Please see above.

Immunogenicity

No immunogenicity issues were reported in the study SYM-1219-401.

8.2.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment data were collected for safety.

8.2.7. Safety Analyses by Demographic Subgroups

There were too few TEAEs to determine an association between any particular TEAE and any age group, race, or ethnicity.

8.2.8. Specific Safety Studies/Clinical Trials

In sNDA S-016, adolescent males aged 12 years to less than 18 years of age are proposed to be included in the indication for the treatment of trichomoniasis. There were no males included in the phase 3 study of SOLOSEC for the treatment of trichomoniasis (SEC-WH-301); however, the safety assessment of SOLOSEC in adult males with trichomoniasis was supported by the safety findings from study SEC-WH-301 in adult females and additional safety information from phase 1 studies of SOLOSEC enrolling healthy males, and from published studies of secnidazole for treatment of males with trichomoniasis. The following sources of data were used to assess the safety of SOLOSEC in adolescent males with trichomoniasis in this review:

- Clinical data from the study of SOLOSEC for the treatment of BV in adolescent females (SYM-1219-401; submitted in S-014 and reviewed in Section 8.2.4)

- Clinical data submitted in the initial NDA consisting of two safety/PK Phase 1 studies with secnidazole that included healthy male volunteers.

    - In study SYM-1219-104, 8 healthy males received doses of secnidazole ranging

from 4 grams to 6 grams. One male subject who received 6 grams of secnidazole reported an adverse event of upper respiratory infection which was mild, not related to the treatment, and resolved. There were no serious adverse events reported.

- In study SYM-1219-105, 30 healthy males received doses of secnidazole ranging from 2 grams to 6 grams. The observed secnidazole plasma concentrations and exposures in males appeared to be slightly lower than those observed in females. In male subjects, after a 2 gram dose of secnidazole, cough (not related) occurred in 2 subjects. Diarrhea (treatment related), hematoma (not related), and pyrexia (not related) were reported in 1 subject each. In the 6 gram dose group of secnidazole, cough (not related), oropharyngeal pain (not related), presyncope (not related), viral infection (not related), and vomiting (treatment related) were reported in 1 subject each. No SAEs or deaths were reported. All AEs were mild in intensity and resolved.

- Four published studies evaluating the use of secnidazole for the treatment of trichomoniasis in males (submitted in S-012 and S-016, reviewed in Section 8.1.4). In the four open-label studies, a total of 211 males received secnidazole. Two studies, (Videau *et al.* and Siboulet *et al.*) included adolescents aged 15 years and older and 12 years and older, respectively. Both were uncontrolled studies. In these two studies, the following adverse events were reported; Videau *et al.*: nausea in 4% of the patients; Siboulet *et al*.: nausea/gastralgia in 8.9% of patients, and gastric burning in 2 patients (1.1%).

The safety findings reported from these sources are generally consistent with the adverse reactions reported following treatment with SOLOSEC for BV in adult females and trichomoniasis in adult females and males in the current labeling. Therefore, the safety profile of SOLOSEC is not expected to differ significantly between males and females. Since the pathophysiology of trichomoniasis is the same in adults and adolescents and the pharmacokinetics of secnidazole are expected to be similar, the safety profile of SOLOSEC is not expected to differ significantly between adolescent males and adult males.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new information regarding carcinogenesis and mutagenesis was submitted.

Human Reproduction and Pregnancy

No new information regarding human reproduction and pregnancy was submitted. The safety study of SOLOSEC in adolescents with BV (SYM-1219-401) excluded women who were pregnant, attempting to conceive or lactating. However, one patient became pregnant during

the study. The patient had a negative urine pregnancy test on Study Day 1 (which was the day of SOLOSEC treatment) then had a positive urine pregnancy test at the TOC visit on Study Day 7. The patient did not experience any adverse events during the course of her pregnancy and delivered a healthy female infant (Apgar score of 8/9, weight 3.04 kg) without any complications at 40 weeks of gestation. A follow-up assessment conducted one-month post-delivery confirmed that the infant did not experience any adverse events.

Pediatrics and Assessment of Effects on Growth

No assessment of effects on growth were made.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

With a single dose, no withdrawal or rebound effects have been observed; no such effects are anticipated. No overdoses occurred in the adolescent BV study SYM-1219-401. As patients were provided with a single unit dose that was typically administered in the clinic, there was minimal potential for abuse or misdose.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

During the course of the review of these sNDAs, a safety labeling change notification was issued to add a contraindication for the use of nitroimidazole antimicrobial drugs, including SOLOSEC, in patients with Cockayne syndrome due to the risk of severe, irreversible hepatotoxicity in this population. Labelling modifications to convey this risk were approved on December 15, 2021.

Expectations on Safety in the Postmarket Setting

No additional safety issues have been identified in the course of this review. Routine postmarket safety surveillance is recommended.

8.2.11. Integrated Assessment of Safety

The assessment of the safety of SOLOSEC in the treatment of BV in adolescent females aged 12 years to less than 18 years is primarily based on the clinical study SYM-1219-401 which evaluated the safety of a single oral dose of SOLOSEC 2 g granules in 40 post menarchal adolescents with bacterial vaginosis. Out of 40 patients, 3 patients (7.5%) reported 4 AEs. Two AEs (nausea and upper abdominal pain) were related to SOLOSEC and occurred in the same patient. All AEs were mild in intensity. No deaths, serious AEs, or discontinuations due to an AE were reported. Also, no clinically significant changes in vital signs, physical examination findings, or laboratory results were reported. The safety profile of SOLOSEC in adolescents in this study was consistent with the safety profile in adults.

The assessment of the safety of SOLOSEC in the treatment of trichomoniasis in adolescent females aged 12 years to less than 18 years is based on the safety data from study SYM-1219-401. Since the doses of SOLOSEC for the treatment of trichomoniasis and BV are identical and both infections present with common symptoms of vulvovaginitis, it is expected that the safety profile of SOLOSEC in the treatment of trichomoniasis in adolescent females would be similar to that of adolescent females being treated for BV. To assess the safety of SOLOSEC in the treatment of trichomoniasis in adolescent males, the reviewers relied upon the safety data from study SYM-1219-401 in addition to the safety data used to support the approval of SOLOSEC for the treatment of adult males, including two Phase 1 studies, SYM-1219-104 and SYM-1219-105, that enrolled healthy male subjects and published studies of the treatment of trichomoniasis in males using secnidazole. Since the pharmacokinetics of secnidazole are expected to be similar in adults and adolescents, it is not anticipated that the safety profile of secnidazole would be significantly different between adult and adolescent males.

8.3. Statistical Issues

Comparative efficacy data in the treatment of BV for the adolescent female population is not available as the single trial conducted (SYM-1219-401) was an uncontrolled study. Furthermore, the sample size of the study was small, and the study was designed primarily to assess safety in the pediatric population. Evidence of efficacy in the adolescent female population is primarily based on extrapolation from the adult population for this indication.

8.4. Conclusions and Recommendations

The reviewers conclude that the Applicant has submitted adequate evidence to recommend the approval of SOLOSEC as a safe and effective treatment for adolescent females aged 12 years to less than 18 years with bacterial vaginosis (BV). The determination of the effectiveness of SOLOSEC in the treatment of BV in adolescent females is primarily based on extrapolation of efficacy data from controlled trials of SOLOSEC for treatment of BV in adult females. The assessment of the safety of SOLOSEC in the treatment of BV in adolescent females is primarily based on data from the adolescent clinical study SYM-1219-401. In this study, the safety profile of SOLOSEC was consistent with that in adults and no new safety signals were identified.

The reviewers conclude that the Applicant has submitted adequate evidence to recommend the approval of SOLOSEC as a safe and effective treatment for adolescent patients aged 12 years to less than 18 years with trichomoniasis. The determination of the effectiveness of SOLOSEC for the treatment of trichomoniasis in adolescent patients is primarily based on extrapolation of the efficacy data from a controlled trial of SOLOSEC in the treatment of trichomoniasis in adult females. Since trichomoniasis is a less severe disease in males than females and is often self-limited, the efficacy data from females were extrapolated to males with supporting evidence from the published scientific literature. The assessment of the safety of SOLOSEC in the

treatment of trichomoniasis in adolescent females is primarily based on the safety of SOLOSEC in the treatment of BV in adolescent females demonstrated in study SYM-1219-401. To assess the safety of SOLOSEC in the treatment of trichomoniasis in adolescent males, the reviewers relied upon the safety data from study SYM-1219-401 in addition to the safety data used to support the approval of SOLOSEC for the treatment of adult males, including two Phase 1 studies, SYM-1219-104 and SYM-1219-105, that enrolled healthy male subjects and published studies of treatment of trichomoniasis in males using secnidazole.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. An Advisory Committee was not convened and there were no external consultations.

10 Pediatrics

The current submissions address the safety and effectiveness of SOLOSEC for the treatment of BV in adolescent females aged 12 to less than 18 years old (S-014), and trichomoniasis in adolescents aged 12 to less than 18 years old (S-016). The safety and effectiveness of SOLOSEC in pediatric patients below the age of 12 years have not been established. The Applicant requested a partial waiver for all BV and trichomoniasis studies in males and in females ages birth to <12 years because studies would be impossible or highly impractical.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following significant changes were made to specific sections/subsections of the prescribing information (PI) submitted by the Applicant on March 29, 2021 (S-014) and August 30, 2021 (S-016):

Section/subsection	Applicant Proposed Labeling	Labeling Modifications
HIGHLIGHTS Recent Major Changes subsection	(b) (4)	Indications and Usage, Bacterial Vaginosis (1.1) XX/2022 Indications and Usage, Trichomoniasis (1.2) XX/2022
FULL PRESCRIBING INFORMATION		
Bacterial Vaginosis (1.1)	(b) (4)	SOLOSEC is indicated for the treatment of bacterial vaginosis in female patients 12 years of age and older *[see Use in Specific Populations (8.1)* and *Clinical Studies (14)].*
Trichomoniasis (1.2)		SOLOSEC is indicated for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in patients 12 years of age and older. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, treat partners of infected patients simultaneously in order to prevent reinfection *[see*

	(b) (4)	*Dosage and Administration (2.2) and Clinical Studies (14.2)]*.
***Clinical Reviewer comment**: The definitions of adult and adolescent can be confusing. Therefore, the reviewer recommended changing the phrases (b) (4) " to "patients" and (b) (4) to "female patients" throughout the Prescribing Information(PI) and Patient Package Insert (PPI)*		
Vulvovaginal Candidiasis (5.1)	(b) (4)	In a controlled clinical trial of non-pregnant female patients with trichomoniasis…
***Clinical Reviewer comment**: Revised the statement for clarity.*		
Clinical Trials Experience (6.1)	• (b) (4) • For trial 5 (the study in female patients treated with SOLOSEC for trichomoniasis), the Applicant revised: (b) (4) to: "The mean age of the patients in this study was 37.7 years, with a range of 15 to 65 years"	• Previous BV studies included adolescent patients. Therefore, instead of having a (b) (4) he clinical trial information for BV in adolescent patients (SYM-1219-401) was added as trial 4 and listed with the other BV studies.
***Clinical Reviewer comment**: The Applicant's revision of the statement regarding trial 5 is acceptable. Previously, the indication for treatment of trichomoniasis was only for adults, and in trial 5, only patients aged 19 to 65 years received SOLOSEC while there were subjects in the placebo group ranging from 15 to 18 years of age.*		
Pediatric Use (8.4)	(b) (4)	Revised to specify how the safety and effectiveness of SOLOSEC for BV and trichomoniasis in pediatric patients aged 12 to 17 years old were established.
Bacterial Vaginosis (14.1)		(b) (4)

***Clinical Reviewer comment**: The pediatric labeling guidance recommends including studies that provide substantial evidence of effectiveness for use in pediatric patients in the Clinical Studies section.* (b) (4) *Substantial evidence of effectiveness is based on extrapolation from the already described adult studies; refer to Section 6.2 (summary of Clinical Pharmacology Assessment , 7.2.1 (Treatment of Bacterial Vaginosis) and 7.2.2 (Treatment of Trichomoniasis) of this review.*

The addition of the basis of approval for the pediatric use of SOLOSEC for the treatment of BV and trichomoniasis was also based on the labeling recommendations in the Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good).

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

No postmarketing requirements and commitments are recommended.

14 Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):
A Multi-Center, Open-Label Study to Evaluate the Safety of a Single Oral Dose of Solosec™ (secnidazole) 2g Oral Granules for the Treatment of Adolescent Girls with Bacterial Vaginosis (Trial SYM-1219-401)

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 70		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒ See section 8.1.2.	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

DEBORAH WANG
01/19/2022 11:01:36 AM

SHUKAL BALA
01/19/2022 11:14:27 AM

AVERY C GOODWIN
01/19/2022 11:15:26 AM

CRISTINA M MIGLIS
01/19/2022 11:19:31 AM

DAKSHINA M CHILUKURI
01/19/2022 11:21:16 AM

CHERYL A DIXON
01/19/2022 11:23:58 AM

KAREN M HIGGINS
01/19/2022 11:28:21 AM

JAE H HONG
01/19/2022 11:29:49 AM

SHRIMANT MISHRA
01/19/2022 12:09:11 PM

HEIDI L SMITH
01/19/2022 12:41:21 PM

GREGORY F DIBERNARDO
01/19/2022 12:50:43 PM

MAUREEN P DILLON PARKER
01/19/2022 01:10:14 PM

ABIMBOLA O ADEBOWALE
01/19/2022 01:18:25 PM

DMITRI IARIKOV
01/19/2022 02:26:23 PM

PETER W KIM
01/19/2022 02:29:15 PM