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Drug Class Review: Vaginal Antibiotics

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Purpose for Class Review:
This is the first drug class review for vaginal antibiotics, prompted by the approval of secnidazole, a new oral therapy approved in 2017 for bacterial vaginosis (BV).

Research Questions:
1. In patients with BV or trichomoniasis, what is the comparative evidence for the effectiveness of vaginal antibiotics based on efficacy outcomes (e.g., clinical resolution, recurrence, symptom resolution)?
2. In patients with BV or trichomoniasis, what is the comparative evidence for the harms of vaginal antibiotics?
3. Are there subpopulations of patients requiring vaginal antibiotics for which specific therapies may be more effective or associated with less harm?

Conclusions:
- This drug class review is limited by lack of high quality evidence. A majority of the evidence comes from studies with small sample sizes, unclear risk of bias (in part due to older studies with methodological challenges), industry funding, and limited number of trials; therefore, strong conclusions of comparative efficacy cannot be made. There is insufficient comparative evidence in women with BV or trichomoniasis that newer treatments or treatments with shorter days of therapy are superior to older therapies or therapies requiring longer treatment durations. Oral metronidazole and tinidazole have Boxed Warnings for possible association with carcinogenicity in mice and rats and oral clindamycin has a Boxed Warning for *clostridium difficile* associated diarrhea.
- Metronidazole and clindamycin have the most evidence for the treatment of BV in non-pregnant women and are recommended first line by Centers for Disease Control (CDC) guidelines (low to moderate quality of evidence).[1,2] There is insufficient evidence that one oral or topical treatment for BV is superior to another.
- There is no data to support the treatment of sexual partners of women with symptomatic BV. Studies showed no benefit of clinical or symptomatic improvement (high strength of evidence).[3]
- There is low strength of evidence from one, small, phase 3 trial that a single dose of oral secnidazole is more effective than placebo in eradication of BV with an ARR of 34% and NNT of 3 at day 21-30 of follow-up.[4]
- In pregnant women with BV, there is low quality evidence that antimicrobial treatment is effective for bacterial eradication, but there is insufficient evidence to show that treatment impacts pregnancy outcomes (preterm birth, late miscarriage).[5]
- In women with trichomoniasis, treatment with nitroimidazole antimicrobials results in higher cure rates compared to no treatment (low strength of evidence). There is insufficient evidence of one nitroimidazole superiority over another.[6]

- The UK treatment guidelines recommend metronidazole, 1-7 days of treatment, as first line therapy for women with trichomoniasis based on high quality evidence.[7]

Recommendations:
- Recommend non-preferred drugs in the class be subject to the Preferred Drug List – Non-Preferred Drugs in Select PDL Class prior authorization (PA) criteria (**Appendix 3**).
- Recommend at least one metronidazole and clindamycin formulation be preferred. Recommend secnidazole be designated as non-preferred.
- After evaluation of comparative drug costs in executive session, make clindamycin phosphate cream, clindamycin phosphate suppositories, and metronidazole gel preferred on the PDL. Make all other agents non-preferred.

Background:
Bacterial vaginosis is an infection that is common in women of reproductive-age (ages 14-49 years) which occurs in approximately 29% of the general population.[8] BV is most often caused by the following bacteria: *Gardnerella vaginalis*, *Prevotella* species, *Porphyromonas* species, *Bacteroides* species, *Peptostreptococcus* species, *Mycoplasma hominis* and *Ureaplasma urealyticum*. Amsel's criteria is often used for diagnosis, which requires 3 of the 4 following criteria: vaginal pH >4.5, release of fishy smell on the addition of alkali (10% potassium hydroxide), characteristic discharge on examination, and presence of 'clue cells' on microscopy of vaginal fluid mixed with normal saline.[1,9] A Gram-stained vaginal smear is also used for diagnosis. The Nugent scoring system (NSS) is a validated method to determine the presence of BV by interpretation of a Gram stain of vaginal secretions.[10] Scores of 0-3 are considered normal, with a positive test indicated by a score of 7 to 10.[8]

Infections can be asymptomatic or symptomatic, with treatment recommended for symptomatic women with the goal of symptom elimination. In pregnant women, preterm delivery is higher in women with BV; however, treatment of asymptomatic infections has not shown to decrease the risk of preterm birth.[8] Therefore, universal screening for BV in pregnant women is not recommended; however women diagnosed with BV during pregnancy should be treated. Women who are asymptomatic and are undergoing an abortion or hysterectomy should also be treated to prevent postoperative infections.[8] The presence of BV is thought to increase the risk of other sexually transmitted diseases (i.e., human immunodeficiency virus, herpes simplex virus type 2, gonorrhoeae, chlamydia and trichomoniasis).[10] Treatment of sexual partners of women with BV is not recommended.

Common therapies to treat BV are metronidazole or clindamycin orally or intravaginally, with cure rates of up to 70% to 80%.[1] Seven days of oral treatment is recommended for metronidazole versus five days of vaginal therapy. A single-dose intravaginal metronidazole dose is available, but the effectiveness compared to multiple day regimens is unknown. Clindamycin is available as a seven-day course of intravaginal cream, seven days of oral therapy, clindamycin ovules for three days and a one-day bioadhesive treatment. The treatment of choice is the seven-day intravaginal regimen as the other delivery options are thought to be associated with a lower incidence of eradication of BV.[1] Oral metronidazole or oral clindamycin are recommended for symptomatic patients who are pregnant. Choice of regimen is dependent upon medication adverse events, cost, patient preference and route of administration. Oral delivery methods are more convenient but are associated with a higher incidence of systemic adverse events including headache, nausea and vomiting. Important outcomes for BV treatments include eradication of symptoms and cure rates.

Alternative treatment options include tinidazole and secnidazole. They should be given as 1 gm for 5 days.[11] Shorter courses of higher doses are used, but are associated with more side effects and reduced efficacy. Secnidazole has been recently approved as a single-dose option with similar eradication rates as metronidazole.[12] There is insufficient evidence to recommend the use of probiotics for adjunctive treatment or the primary treatment of BV.[8]

In addition to BV, vaginal antibiotics are used for trichomoniasis, which is a flagellated protozoan (*T.vaginalis)* which may infect the urogenital tract. Detection of *T.vaginalis* is done microscopically. Newer monoclonal antibody-based point of care testing and nucleic acid amplification test (NAAT) detect trichomoniasis with a high degree of sensitivity but are not used routinely in clinical settings.[2,13] Trichomoniasis is the most common non-viral sexually transmitted disease, affecting approximately 3.7 million persons.[8] Coinfections with BV is common in women with rates as high as 80%. Prevalence of trichomoniasis in the United States is thought to range from 1.3% (non-Hispanic white women) and to up to 13.3% (non-Hispanic black women). Discharge, burning and pain are common symptoms with trichomoniasis; however, asymptomatic carrier infections are also common. Diagnosis is made by a laboratory test confirming the presence of trichomoniasis. Treatment of trichomoniasis is recommended to prevent the development of urethritis or cystitis. Increased risk of acquiring HIV may occur if trichomoniasis remains untreated, in addition to an increase in the incidence of cervical intraepithelial neoplasia and cervical carcinoma.[13] The rate of preterm birth and other undesirable obstetric outcomes have been seen in pregnant women with trichomoniasis.

Patients experience a spontaneous cure in up to 25% of trichomoniasis cases and only approximately 5% of cases develop resistance.[13] Treatment of asymptomatic and symptomatic women and men is recommended to prevent transmission to sexual partners. Partners should also be evaluated and treated. Treatment regimens recommended for trichomoniasis are a single 2 gm dose of either oral metronidazole or tinidazole. Cure rates are as high as 88% with metronidazole after a single dose versus 92% for a 5-7 day course.[13] The recommended regimen for pregnant women is 2 grams orally of metronidazole or 500 mg twice daily for 5-7 days. Patients with HIV should be treated twice daily for seven days.

The vaginal antibiotic class has a low volume of claims and represents only a small percentage of overall cost burden to the Oregon Health Plan (OHP) system. The only drug with a non-preferred designation is the branded metronidazole vaginal gel, Nuvessa, which had no utilization last quarter. Eighty-five percent of the utilization is for generic metronidazole gel.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Lincosamides			
Clinidamycin[14]	BV	300 mg orally	1 capsule twice daily for 7 days
Clindaymcin[15]	BV	100 mg vaginally	1 suppository for 3 or 7 days
Clindamycin (Clindesse)[16]	BV	100 mg vaginally	1 suppository as one dose
5-Nitro-imidazoles			
Metronidazole[17]	BV or trichomoniasis	500 mg orally	1 tablet twice daily for 7 days
Metronidazole[18]	BV or trichomoniasis	37.5 mg vaginally	1 applicator once daily for 5 days
Metronidazole (Nuvessa)[19]	BV or trichomoniasis	65 mg vaginally	1 applicator at bedtime
Tinidazole[11]	Trichomoniasis	2 grams	As one dose
Tinidazole[11]	BV	1- 2 grams orally	2 grams as one dose or 1 gram for 5 days
Secnidazole[12]	BV	2 grams orally	1 packet of granules as a single dose

Abbreviations: BV = bacterial vaginosis

Table 2. Summary of Pivotal Studies Completed.

Study	Comparison	Population	Primary Outcome	Results
Schwebeke, et al[4] Phase 3, RCT, PC	Secnidazole 2 gm granules X 1 dose (S) vs. Placebo granules X 1 dose (P)	Non-pregnant women mean age of 31 years with BV(n=189)	Proportion of clinical outcome responders at follow-up visit days 21-30*	S: 57 (53%) P: 11 (19.3%) ARR 34%/NNT 3; p<0.001
Hillier, et al[20] Phase 2, RCT, DB, PC^	Secnidazole 1 gm granules X 1 dose (S1) vs. Secnidazole 2 gm granules X 1 dose (S2) vs. Placebo granules (P)	Adult women with a median age of 33 years and BV	Clinical cure 21-30 days after treatment*	S1: 33 (51.6%) S2: 42 (67.7%) P: 11 (17.7%) S1 vs. P: ARR 34%/NNT 3; p<0.001 S2 vs. P: ARR 50%/NNT 2; p<0.001
Key: * Clinical outcome responders defined as: normal vaginal discharge, negative 10% potassium hydroxide whiff test and Clue cells <20% of total epithelial cell count on microscopic examination of the vaginal wet mount, using saline as the test of cure/end of study visit ^ Used for FDA approval				
Abbreviations: ARR – absolute risk reduction; BV – bacterial vaginosis, DB – double-blind; NNT – number needed to treat; PC – placebo controlled; RCT – randomized controlled trial				

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Bacterial Vaginosis

Cochrane – Antibiotic Treatment for the Sexual Partners of Women with Bacterial Vaginosis

A 2016 Cochrane review identified seven randomized controlled trials with 1026 participants.[3] Five trials were placebo controlled and two trials had no comparator. Nitroimidazoles were used for treatment in six trials, four trials used metronidazole and two trials used tinidazole. Patients were sexual partners of

adult women between the ages of 17-56 years with symptomatic BV.[3] Four trials were industry funded. Most studies had a low risk of bias for random sequence generation, blinding and outcome assessment. Seventy-five percent of studies had an unclear risk of allocation concealment. Primary outcomes were BV recurrence, clinical improvement (based on Amsel's criteria or other clinical criteria), symptomatic improvement and serious adverse events.

High quality evidence found clinical improvement in women at week 1-4 of follow-up to be similar with antibiotic treatment compared to placebo (RR 1.02; 95% CI, 0.94 to 1.11). Results were also similar at week 4-12 of follow-up (RR 0.98; 95% CI, 0.90 to 1.07).[3] Symptomatic improvement during the first week was similar with treatment and placebo (RR 1.06; 95% CI, 1.00 to 1.12; 3 studies) based on high quality evidence. Recurrence of BV after 4 weeks was not different between antimicrobial treatment and placebo in women, as demonstrated by a RR of 1.0 (95% CI, 0.67 to 1.52; 3 studies); however, evidence was considered to low quality.[3] Sexual partners report an increased incidence of adverse reactions. Limitations to the evidence included limited number of trials for each comparison and risk of publication bias due to industry funding of studies.

Cochrane – The Effects of Antimicrobial Therapy on Bacterial Vaginosis in Non-Pregnant Women
A Cochrane review in 2010 reviewed the evidence for the use of antimicrobials for the treatment of BV in adult women who were not pregnant.[1] Twenty-four trials were identified that evaluated the following antibiotics: clindamycin (topical and oral), metronidazole (oral and topical), secnidazole, triple sulfonamide cream, hydrogen peroxide douche, and oral lactobacillus. Tinidazole was included in the search criteria but no studies were included. Nine of the 24 were funded by industry. Patients ranged from 15-75 years and all had a diagnosis of symptomatic BV.[1] The primary outcome was treatment failure determined by the Amsel criteria at 7-30 days after treatment. The evidence was assessed for risk of bias but was not given an overall evidence grade by Cochrane.

Results for the outcome of clinical failure that resulted in either a) analysis of 2 or more studies b) were statistically significant are presented in **Table 3**.[1] Comparisons of individual studies that resulted in insufficient evidence to draw conclusions on clinical cure rates resulted from the following comparisons: clindamycin ovule versus clindamycin cream, clindamycin ovule versus lactobacilli, clindamycin cream versus oral tinidazole, 2% clindamycin cream versus triple sulfonamide cream, polyhexamethylene biguanide douche versus clindamycin cream, cefadroxil versus metronidazole, secnidazole 1 gm versus secnidazole 2 gm, and lactobacillus versus metronidazole.[1] Limitations to the evidence includes small study sample sizes, multiple studies with unclear risk of bias in randomization and allocation, large confidence intervals and high heterogeneity in some of the meta-analyses.

Table 3. Clinical Failure Results for Antimicrobial Therapy for Bacterial Vaginosis.[1]

Comparison	Number of studies/patients	Limitations	Results for clinical failure	Adverse events
Topical metronidazole vs. Placebo (P)	2/191	• Small study size • Unclear allocation bias in both studies	TM: 44 (36%) P: 45 (66%) RR 0.59 (95% CI, 0.44 to 0.79) *Favors of metronidazole*	Candida infection: TM: 6 (16%) P: 0 (0%) ARR 16/NNH 7
Topical clindamycin (TC) vs. Placebo (P)	2/285	• Small study size • Unclear randomization in both studies • Unclear allocation concealment in one study	TC: 18 (12%) P: 64 (50%) RR 0.19 (95% CI, 0.09 to 0.41) *Favors of clindamycin*	Not reported

Metronidazole (M) vs. Clindamycin (C)	6/1189	• Unclear allocation concealment (4 studies) • Unclear randomization allocation (2 studies) • One open-label study	M: 48 (8%) C: 51 (9%) RR 1.06 (95% CI, 0.64 to 1.75) *No significant difference between treatments**	Metallic taste: 0.09 (95% CI, 0.01 to 0.68) Nausea/vomiting: 0.27 (95% CI, 0.11 to 0.69)
Tinidazole vs. Metronidazole	2/175	• Both studies open-label with unclear randomization allocation • High heterogeneity (I^2= 42%)	*No significant difference between treatments*	Rates of nausea and vomiting were similar
Oral metronidazole (OM) vs. Clindamycin cream (CC)	3/528	• Unclear allocation concealment in 2 studies • High heterogeneity (I^2= 40%)	OM: 17 (6%) CC: 26 (10%) RR 1.43 (95% CI, 0.57 to 3.60) *No significant difference between treatments*	Metallic taste: RR 0.08 (95% CI, 0.1 to 0.59) Nausea and vomiting: RR 0.23 (95% CI, 0.10 to 0.51)
Single hydrogen peroxide douche (HP) vs. Single dose metronidazole (M)	1/142	• Low risk of bias for all domains	HP: 27 (38%) M: 15 (21%) ARR 17/NNT 6 RR 1.75 (95% CI, 1.02 to 3.00) *Favors metronidazole*	Reduced eating and vomiting: HP: 10 (14%) M: 34 (62%) vaginal irritation: HP: 24 (33%) M: 10 (14%)
Metronidazole vs. Metronidazole + azithromycin	3/554	• Low risk of bias for all domains	M: 36 (27%) M+A: 75 (18%) RR 0.65 (95% CI, 0.46 to 0.92) *Favors metronidazole + azithromycin*	Incidence of candida and nausea were similar in both groups

Cochrane – Antibiotics for Treating Bacterial Vaginosis in Pregnancy

A 2013 review assessed the efficacy of antimicrobial therapies in women who were pregnant with a diagnosis of asymptomatic or symptomatic BV.[8] Twenty-one trials (n=7847 women) of good quality with an overall low risk of bias were included in the review. Inclusion criteria required a Nugent score of at least 4, suggesting inclusion of borderline BV infection and patients with a BV diagnosis. Evidence was identified for the following treatments: metronidazole and clindamycin. Data was analyzed for risk of bias, but overall evidence grades were not provided. Bacterial eradication, risk of late miscarriage, and incidence of pre-term birth were the main outcomes of interest.

Results for the primary outcomes are presented in **Table 4**.[8] All other outcomes were based on very low quality evidence, primarily limited studies of small sample size. There was no difference identified in the following subgroup analyses: preterm birth before 34 weeks, 32 weeks or low birthweight. Similar limitations as described in the above Cochrane review are applicable to this review as well. Unfortunately, high quality evidence for BV treatment is lacking.[8]

Table 4. Outcomes in Pregnant Women Treated for Bacterial Vaginosis.[8]

Outcome	Number of studies/patients	Comparison	Results	Limitations	Adverse events
Preterm Birth*	13/6491	Any antimicrobial vs. Placebo	RR 0.88 (95% CI, 0.71 to 1.09) *No significant difference between treatments*	Moderate heterogeneity (I^2= 48%)	Higher incidence of adverse events compared to placebo
	1/258	Oral metronidazole + erythromycin vs. Placebo	RR 0.64 (95% CI, 47 to 0.88) *Favors metronidazole + erythromycin*	One small study	Same as above
Late Miscarriage	2/1270	Any antimicrobial vs. Placebo	RR 0.20 (95% CI, 0.05 to 0.76) *Favors antimicrobial treatment*	NR	Same as above
Failure of Test of Cure (eradication failure)	10/4403	Any antimicrobial vs. Placebo	RR 0.42 (95% CI, 0.31 to 0.56) *Favors antimicrobial treatment*	High heterogeneity (I^2=91%)	Same as above
Key: * Defined as before 37 weeks					
Abbreviations: CI – confidence interval; NR – not reported; RR – risk ratio					

Trichomoniasis

Cochrane – Interventions for Treating Trichomoniasis in Women

A 2009 review assessed the treatment of symptomatic and asymptomatic trichomoniasis (confirmed by laboratory testing) in women who were not pregnant.[13] Fifty-four trials were identified, 30 had moderate risk of allocation concealment bias, 16 had low risk and 8 had high risk. Outcome assessment was blinded in 13/54 trials and was unclear in the remaining trials. Evidence was identified for treatments of miconazole, ornidazole (not available in the US) and tinidazole. All studies were small, enrolling less than 200 patients in most studies. Studies were assessed for risk of bias, but the evidence was not given an evidence grade.[13]

Evidence supports the higher cure rates with antimicrobials compared to placebo (**Table 5**).[13] Use of any nitroimidazole resulted in parasitological cure, regardless of treatment course duration. Limitations to the systematic review and meta-analysis include small sample size, limited number of studies, high attrition rates and lack of comparative efficacy studies between treatments.

Table 5. Cure Rates of Trichomoniasis Treatment with Nitroimidazoles^ in Women.[13]

Outcome	Number of studies/patients	Comparison	Results	Limitations	Adverse events
No Parasitological Cure (day 4 to 4 weeks)	6/672	Treatment vs. No treatment	RR 0.19 (95% CI, 0.15 to 0.23) *Favors treatment*	High heterogeneity (I^2=96%)	Metallic taste, nausea and vomiting were more common with treatment

No Parasitological Cure (f/u day not stated)	4/427	Short treatment (1-2 doses) vs. Long treatment (5-10 days)	RR 1.12 (95% CI, 0.58 to 2.16) *No significant difference between treatments*	Moderate heterogeneity (I^2=29%)	Short term treatment associated with a higher rate of adverse events
No Parasitological Cure (2 weeks)	4/426	Oral + intravaginal treatment vs. Oral treatment	RR 3.00 (95% CI, 1.10 to 8.16) *Favors combination treatment*	Individual trials were small	Not studied
Key: ^ metronidazole, tinidazole and ornidazole Abbreviations: CI – confidence interval; RR – risk ratio					

Cochrane – Interventions for Trichomoniasis in Pregnancy
A 2011 Cochrane review found insufficient evidence to determine the effect of treating trichomoniasis on pregnancy outcomes.[21]

Guidelines:
Centers for Disease Control – Sexually Transmitted Diseases Treatment Guidelines
In 2015, the CDC released new guidance on treatment recommendations for sexually transmitted disease.[8] Guidelines were authored by workgroup members from federal, state, and local health departments; clinical providers; and professional organizations. The chair had no conflicts of interest; however, sixteen of the workgroup members have conflicts with industry. A systematic review of the literature was performed and the literature was graded using the United Services Preventative Services Task Forces (USPSTF) modified rating system. Recommendations were reviewed by a second independent panel of public health and clinical experts. Evidence tables and assessment of the individual studies were provided; however, individual grades of the evidence were not provided for evidence pertaining to BV.

Table 6. United Services Preventative Services Task Forces (USPSTF) Modified Rating System.[8]

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

CDC guidelines recommend treatment of symptomatic women with BV to relieve symptoms and reduce the risk of acquiring *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, HIV and herpes simplex type 2.[8] Recommended treatment options are presented in **Table 7,** and alternative treatments are presented in **Table 8**. Recurrence may be treated with the same regimen or an alternative therapy. For multiple recurrences, guidelines recommend 0.75% metronidazole gel twice weekly for 4-6 months. Other suppressive options include seven days of metronidazole or tinidazole followed by intravaginal boric acid 600 mg daily for 21 days followed by 0.75% metronidazole gel twice weekly for 4-6 months. Monthly 2 gm metronidazole orally with fluconazole 150 mg may also be an option.

Table 7. Bacterial Vaginosis Recommended Treatment Regimens.[8]

Therapy	Dosing Regimen
Metronidazole	500 mg twice daily orally for 7 days
Metronidazole Gel	0.75% applicator intravaginally once daily for 5 days
Clindamycin Cream	2% applicator intravaginally at bedtime for 7 days
Pregnant Women	
Metronidazole	250 mg orally three times daily for 7 days or 500 mg orally twice daily for 7 days

Table 8. Bacterial Vaginosis Alternative Treatment Regimens.[8]

Therapy	Dosing Regimen
Tinidazole	2 gm orally once daily for 2 days
Tinidazole	1 gm orally once daily for 5 days
Clindamycin Ovules	100 mg intravaginally at bedtime for 3 days

Trichomoniasis treatment is used to reduce symptoms as well as transmission. The recommended treatments were based on an evidence grade of A-B (**Table 9**). Similar efficacy and safety of treatment options for trichomoniasis have been demonstrated. A reduced incidence of gastrointestinal side effects has been demonstrated with tinidazole.

Table 9. Treatment Options for Trichomoniasis.[8]

Recommended Therapy		
Metronidazole	2 gm orally in a single dose	84% to 98% cure rates
Tinidazole	2 gm orally in a single dose	92% to 100% cure rates
Alternative Therapy Options		
Metronidazole	500 mg orally twice daily for 7 days	84% to 98% cure rates

United Kingdom National Guideline on the Management of Trichomonas Vaginalis

The British Association for Sexual Health and HIV (BASHH) authored an update to its 2007 guideline on the management of trichomonas in 2014.[13] The guideline is accredited by the National Institute for Health and Care Excellence (NICE) which ensures that the guidelines were created based on the AGREE tool that is used

to distinguish high quality guidelines. The guideline was funded internally and one of 6 authors reported receiving funding from industry. The assignment of strength of evidence is provided in **Table 10,** and the rating scheme is provided in **Table 11**.

Table 10. Levels of Evidence.[13]

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trials
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one type of well-designed quasi-experimental study
III	Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authors

Table 11. Grading of Recommendations. [13]

Grade	Recommendations
A (Evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, II)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Treatment recommendations are presented in **Table 12**.[13] First-line treatment recommendation is for metronidazole given as a single dose or for up to 7 days. Metronidazole is also recommended in women who are pregnant, but high-dose regimens are advised against. Tinidazole is a contraindicated in the first trimester and the safety of use has not been well researched.[13] Limited evidence suggests that single dose regimens of metronidazole are not as effective as metronidazole given twice daily for 7 days in women with HIV. Guidelines recommend a repeat of a 7-day course of standard therapy for patients who are non-responsive to standard therapy (Evidence Level III).[13] A higher dose regimen of nitroimidazole is recommended for patients failing the subsequent regimens (**Table 7**). Guidance recommends the treatment of sexual partners.

Table 12. UK Guidelines for Treatment of Trichomonas.[13]

Treatment	Dose	Evidence Level / Grade
Metronidazole	2 gm orally as a single dose	Ia / A
Metronidazole	400-500 mg twice daily for 5-7 days	Ia / A
Tinidazole (alternative regimen due to cost)	2 gm orally as a single dose	Ia / A
Non-response to standard trichomonas therapy		
Metronidazole	400-500 mg twice daily for 7 days	III
High-dose nitroimidazole for non-responsive trichomonas for patients failing second regimen		

Metronidazole	2 gm daily for 5-7 days	III
Metronidazole	800 mg three times daily for 7 days	III
Tinidazole	2 gm daily for 5-7 days	III
Higher-dose nitroimidazole for non-responsive trichomonas for patients failing third regimen		
Tinidazole	1 gm twice daily or three times daily for 14 days	III
Tinidazole	2 gm twice daily for 14 days	III
Tinidazole intravaginal	500 mg twice daily for 14 days	III

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Appendix 1: Specific Drug Information for Drugs in the Class

Generic	Brand	Route	FormDesc	PDL
clindamycin	CLINDAMYCIN	PO	CAPSULES	
clindamycin phosphate	CLEOCIN	VG	CREAM/APPL	
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	VG	CREAM/APPL	
clindamycin phosphate	CLINDESSE	VG	CRM ER (G)	
clindamycin phosphate	CLEOCIN	VG	SUPP.VAG	
metronidazole	METRONIDAZOLE	PO	TABLET	
metronidazole	METROGEL-VAGINAL	VG	GEL W/APPL	
metronidazole	METRONIDAZOLE	VG	GEL W/APPL	
metronidazole	NUVESSA	VG	GEL W/APPL	N
metronidazole	VANDAZOLE	VG	GEL W/APPL	
tinidazole	TINDAMAX	PO	TABLET	
secnidazole	SOLOSEC	PO	GRANDR PKT	

Table 13. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Clindamycin capsules[14]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	90% when administered orally	CYP3A4 with minor contribution from CYP3A5 forming clindamycin sulfoxide and N-desmethylclindamycin. 10% urine, 3.6% feces and the majority excreted as bioinactive metabolites.	• Half-life: 2.4 hours • Cmax: 2.50 mcg/mL • AUC: Not reported • Vd: Not reported
Clindamycin phosphate vaginal cream[15]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	5% systemic absorption	NA	• Half-life: 1.5 to 2.6 hours • Cmax: 16-18 ng/mL • AUC: Not reported • Vd: Not reported
Clindamycin phosphate vaginal cream (Clindesse®)[16]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	Minimal systemic absorption	NA	• Half-life: Not reported • Cmax: 6.6 ng/mL • AUC: 175 ng/mL • Vd: Not reported
Metronidazole tablets[17]	Nitroimidazole antibacterial that works in an anaerobic	Well absorbed (specific percentage not stated)	60-80% in the urine 6-15% in the feces	• Half-life: 8 hours • Cmax: 6 mcg/mL – 40 mcg/mL (dose dependent)

	environment against most obligate anaerobes.			• AUC: 175 ng/mL • Vd: Not reported
Metronidazole vaginal gel 0.75% and 1.3%[18]	Nitroimidazole antibacterial that works in an anaerobic environment against most obligate anaerobes. The exact mechanism is unknown.	Minimal systemic exposure	NA	• Half-life: Not reported • Cmax: 214-294 ng/mL • AUC: 5,434-5,989 ng•hr/mL • Vd: Not reported
Tinidazole tablets[11]	Antiprotozoal, antibacterial agent	Completely absorbed	CYP3A4 20-25% in the urine 12% in the feces	• Half-life: 12-14 hours • Cmax: 47.7 ng/mL • AUC: 901.6 ng•hr/mL • Vd: 50 L
Secnidazole (Solosec™) granules[12]	Nitroimidazole antimicrobial thought to interfere with bacterial DNA synthesis of susceptible isolates.	Not reported	CYP450 and 15% is excreted in the urine	• Half-life: 17 hours • Cmax: 45.4 mcg/mL • AUC: 1331.6 mcg•hr/mL • Vd: 42 L
Abbreviations: AUC – area under the curve; Cmax – maximum concentration; NA – not applicable; Vd – volume of distribution				

Table 14. Use in Specific Populations.

Drug Name	Use in Renal Impairment	Use in hepatic impairment	Pregnancy
Clindamycin capsules[14]	Half-life may increase slightly in patients with markedly reduced renal function	Moderate to severe liver disease may prolong the half-life	May be used in the second and third trimesters. Use in first trimester only if clearly needed
Clindamycin phosphate vaginal cream*[15]	Not reported	Not reported	May be used in pregnant patients if clearly needed
Metronidazole tablets[17]	May accumulate metronidazole metabolites in end-stage renal disease. Monitor for adverse events.	In severe hepatic impairment (Child-Pugh C) a dose reduction is recommended. Monitor for adverse events in mild to moderate hepatic impairment	Contraindicated in the first trimester of pregnancy
Metronidazole vaginal gel[18]	Not reported	Use caution in severe hepatic disease	No data in pregnant women
Tinidazole tablets[11]	No dosage adjustment for severe renal failure	Use with caution in hepatic impairment	Contradicted in first trimester, not recommended
Secnidazole (Solosec™) granules[12]	Not reported	Not reported	Insufficient data
*** Includes Clindesse® formulation**			

Drug Safety:

Boxed Warnings:
Clindamycin oral: The use of clindamycin has been associated with *Clostridium difficile* diarrhea which may result in mild diarrhea to fatal colitis.
Metronidazole oral: Metronidazole has been shown to be carcinogenic in mice and rats. Use only for indicated conditions.
Tinidazole: Carcinogenicity has not been demonstrated in tinidazole studies, but due to the structural commonalities with metronidazole, tinidazole also has a Boxed Warning for carcinogenicity in mice and rats. Tinidazole should only be used for approved indications.

Risk Evaluation Mitigation Strategy Programs:
None

Contraindications:
Clindamycin: hypersensitivity reactions to clindamycin or history of regional enteritis, ulcerative colitis, or a history of *C. difficile*-associated diarrhea.
Metronidazole: hypersensitivity reactions to metronidazole, concomitant use with disulfiram, concomitant use with alcohol.
Tinidazole: hypersensitivity reactions to tinidazole, first trimester pregnancy, and nursing moms.
Secnidazole: hypersensitivity reactions to secnidazole.

Table 15. Summary of Warnings and Precautions.

Warning/Precaution	Clindamycin capsules	Clindamycin vaginal cream	Metronidazole tablets	Metronidazole vaginal gel	Tinidazole tablets	Secnidazole granules
C. difficile associated diarrhea	X	X				
Anaphylactic and severe hypersensitivity reactions	X					
Use cautiously in patients with a history of bowel disease	X	X				
Use cautiously in atopic individuals	X					
Breakdown of latex or rubber products (i.e., condoms, diaphragms)		X				
May cause fungal infections			X	X	X	X
May cause mild/transient leukopenia			X		X	
May cause transient neutropenia					X	
Carcinogenic in mice and rats			X	X	X	X
Cannot be used with disulfiram or alcohol			X	X	X	
Risk of central and peripheral nervous system effects			X	X		

Hepatotoxicity and death in patients with Cockayne Syndrome			X			
First trimester pregnancy / nursing					X	
Seizures and neuropathy					X	

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to June Week 4 2018
Search Strategy:

#	Searches	Results
1	clindamycin phosphate.mp.	322
2	clindamycin.mp. or CLINDAMYCIN/	10369
3	metronidazole.mp. or METRONIDAZOLE/	16984
4	tinidazole.mp. or TINIDAZOLE/	1311
5	secnidazole.mp.	129
6	1 or 2 or 3 or 4 or 5	26690
7	limit 6 to (english language and humans and yr="2003 -Current")	8456
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	399

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- Ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**No**: Go to #5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *7/15 (RC), 9/10; 9/09; 5/09*
Implementation: *10/13/16; 8/25/15; 8/15; 1/1/11, 9/16/10*