



Development Considerations for a Syndromic Approach to Uncomplicated Urethritis/Cervicitis

FDA-CDC-NIAID Virtual Public Workshop
Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea

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Clinical Considerations in the Development of New Antimicrobials for Gonorrhea

1. Extra-genital infections
2. Co-infections
3. Resistance
4. Gender

- *Chlamydia trachomatis* (20-40%)
- *Mycoplasma genitalium* (25% in men)
- Syphilis, other less common bacterial and protozoan STIs

Most require multiple dose therapy

Indications from Current Antibiotics

ROCEPHIN® (ceftriaxone sodium)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by Neisseria gonorrhoeae, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of Neisseria gonorrhoeae.

1 INDICATIONS AND USAGE

ZITHROMAX (azithromycin) is a macrolide antibacterial drug indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these indications. *[see Dosage and Administration (2)]*

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

To date, no agent has been approved for the treatment of M. genitalium

Development Considerations of Syndromic Treatment for Uncomplicated Urethritis/Cervicitis

- ❑ Antibacterial agents are commonly developed utilizing a syndromic versus pathogen specific approach
 - ❑ Community-acquired bacterial pneumonia, uncomplicated urinary tract infections, acute bacterial skin & skin structure infections
- ❑ Current treatment guidelines for gonorrhea recommend single-dose treatment with a cell wall active agent and recognize the need to assess potential co-infecting pathogens

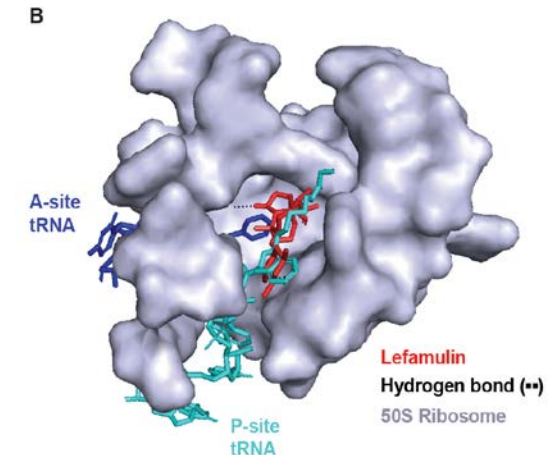
Potential Target Product Profile: Syndromic Treatment of Uncomplicated Urethritis/Cervicitis

- ❑ **Indication:** DRUG X is an antibacterial indicated for the treatment of adults with uncomplicated urethritis or cervicitis caused by the following susceptible microorganisms: *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*
- ❑ **Target Population:** Adults (≥ 18 years) with a diagnosis of uncomplicated urethritis or cervicitis due to *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*
 - ❑ For *N. gonorrhoea* inclusion of concurrent pharyngitis, ano-rectal infection/proctitis dependent on # of subjects enrolled and response
- ❑ **Dosing and Administration:**
 - ❑ XXX mg orally every YY hours
 - ❑ *Neisseria gonorrhoea*: X days
 - ❑ *Chlamydia trachomatis*, *Mycoplasma genitalium*: Y days

Lefamulin

Potential Agent for Syndromic Treatment of STIs

- **Lefamulin is the first IV and oral pleuromutilin approved in the US, Europe, and Canada**
- Derived from pleuromutilin, a naturally occurring antibacterial isolated from an edible mushroom (*Pleurotus mutilus*, now called *Clitopilus scyphoides*)
- Novel mechanism of action at highly conserved core of the ribosomal peptidyl transferase center that results in
 - Low propensity for the development of bacterial resistance *in vitro*
 - Lack of *in vitro* cross-resistance with other antibiotic classes
- Pharmacokinetic profile
 - Rapidly absorbed after oral administration
 - Tissue concentrations \geq those achieved in plasma



Potential of Lefamulin for Treatment of STIs

Potent *In Vitro* Activity Against Most Common Pathogens Associated Urethritis/Cervicitis



Excellent *In Vitro* Activity against MDR STI pathogens^a

Species	<i>n</i>	MIC ₅₀ [mg/L]	MIC ₉₀ [mg/L]	MIC range [mg/L]
<i>Neisseria gonorrhoeae</i>	368	0.25	1	≤0.008 - 2
<i>Mycoplasma genitalium</i> ^b	41	≤0.008	0.06	0.0005-0.06
MDR <i>Mycoplasma genitalium</i> ^c	6	0.06	-	0.016 – 0.06
<i>Chlamydia trachomatis</i>	15	0.02	0.04	0.01 – 0.04
<i>Haemophilus ducreyi</i>	6	-	-	≤0.015 – 0.25
<i>Peptostreptococcus</i> spp.	10	0.06	1	0.03 – 2
<i>Porphyromonas</i> spp.	10	0.03	0.03	0.03
<i>Prevotella</i> spp.	10	0.5	4	0.015 – ≥32

Highly Active Against MDR *M. genitalium*

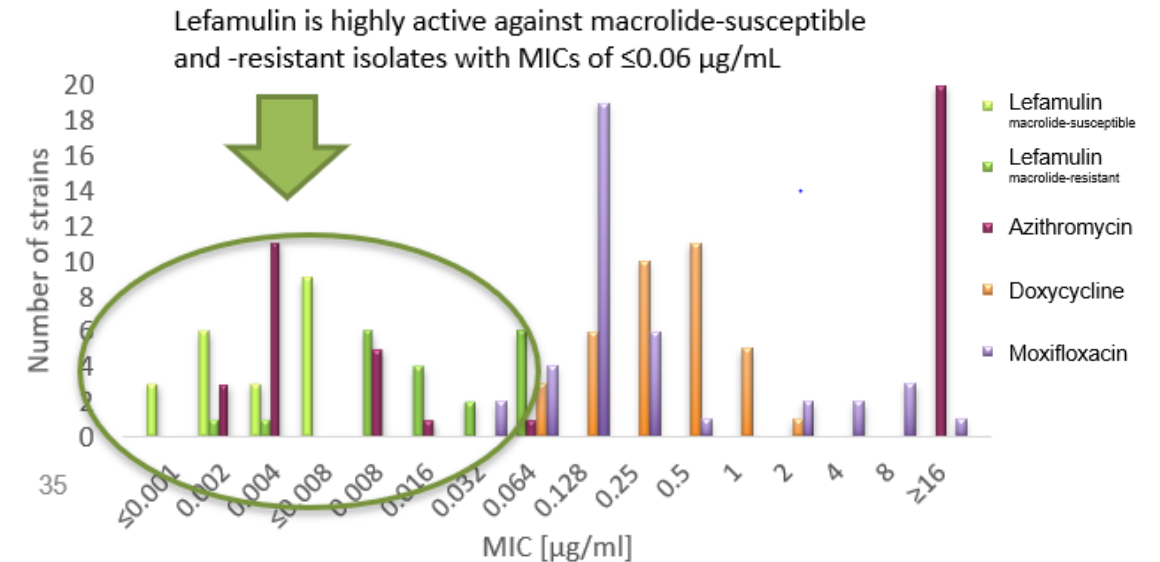


Table:

^a Paukner S, et al. ICAAC 2013 Poster E-1183; Paukner S, et al. Antimicrob Agents Chemother 2018;62(5):e02380-17.

^b n=40 strains macrolide-resistant; n=8 strains moxifloxacin-resistant with n=7 being both macrolide- and moxifloxacin-resistant; Jensen SK, et al. ECCMID 2017 Poster P1335.

^c very recent multi-drug resistant clinical isolates from patients failing treatment with high doses of azithromycin, moxifloxacin, and doxycycline

Lefamulin Distribution in the Male Urogenital Tract in Rats

- High concentrations of [¹⁴C]-Lefamulin were observed in certain glandular tissues (e.g. preputial, bulbourethral) and in the urethra, similar to those in the lung
- At 30 minutes and 6 hours post-dose in the urethra, concentrations were similar, corresponding to 6.6 and 36.6 times higher than in the blood, respectively
- MARG of the prostate gland and seminal vesicles showed higher concentrations of radioactivity associated with the walls (epithelium and mucosa) vs the lumen
- Concentrations in several urogenital tract tissues at 24 hours after administration were similar to those observed in the lung

Concentration of [¹⁴C]-Lefamulin in the urogenital tract of male rats at 0.5, 6 and 24 hours after administration of 30 mg/kg IV

Male Tissue	µg Equivalents*			Tissue: Blood Ratio			Tissue: Lung Ratio		
	0.5 h	6 h	24 h	0.5 h	6 h	24 h	0.5 h	6 h	24 h
Blood	3.4	0.7	BLQ	1.0	1.0	NC	0.1	0.03	NC
Lung	26.5	20.5	0.4	NA	NA	NA	1.0	1.0	1.0
Bulbourethral gland	53.4	13.4	NS	15.8	20.5	NC	2.0	0.7	NC
Preputial gland	NS	15.4	9.8	NC	23.5	NC	NC	0.8	25.9
Prostate gland, whole	11.0	8.4	0.5	3.3	12.8	NC	0.4	0.4	1.3
Prostate gland, lumen	4.6	6.5	0.3	1.4	10.0	NC	0.2	0.3	0.8
Prostate gland, wall	14.4	12.5	0.7	4.3	19.0	NC	0.5	0.6	1.9
Seminal vesicles, whole	8.3	7.6	0.5	2.5	11.6	NC	0.3	0.4	1.2
Seminal vesicles, lumen	2.7	4.2	0.3	0.8	6.5	NC	0.1	0.2	0.8
Seminal vesicles, wall	16.7	10.7	0.6	5.0	16.3	NC	0.6	0.5	1.6
Testis	1.3	2.3	2.0	0.4	3.5	NC	0.1	0.1	5.2
Urethra	22.3	24.0	0.8	6.6	36.6	NC	0.8	1.2	2.1
Urinary bladder, whole	19.5	20.4	0.6	5.8	31.2	NC	0.7	1.0	1.6
Urinary bladder, contents	24.2	35.0	0.9	7.2	53.4	NC	0.9	1.7	2.2
Urinary bladder, wall	8.2	3.4	0.1	2.4	5.1	NC	0.3	0.2	0.2

BLQ=below limit of accurate quantification (<0.062 µg equivalents/g); NA=not applicable; NC=not calculable (tissue is BLQ/NS at this time); NS=no sample, tissue not sectioned.

*Data are µg equivalents of lefamulin per gram tissue

Development Considerations for Syndromic Treatment of Uncomplicated Urethritis/Cervicitis

Target Patient Population

- Adults (≥ 18 years) with a diagnosis of uncomplicated urethritis or cervicitis due to *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*
 - N. gonorrhoea*: inclusion subjects with concurrent pharyngitis, ano-rectal infection/proctitis
 - Inclusion of men and women
- Use of rapid diagnostics to stratify subjects

Choice of comparator and duration of treatment

- Combination therapy for GC + Chlamydia; No approved treatment for *M. genitalium*

Level of evidence to support an indication of adults with uncomplicated urethritis/cervicitis

- Primary endpoint or the TOC date determined by pathogen (eg. negative culture on Day 7 for GC versus negative NAAT on Day 14-21 for *M. genitalium*, *C. trachomatis*)
- If resistant pathogens are identified in such a trial, what level of data would be sufficient for inclusion in the prescribing information?
- Utility of a PRO tool

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