TARGET PRODUCT PROFILES FOR ORAL THERAPY OF URINARY TRACT INFECTIONS

World Health Organization

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Introduction

Disease burden

Urinary tract infections (UTIs) are associated with significant disease burden, antimicrobial resistance (AMR) and cost.

Acute uncomplicated lower UTI, mainly cystitis in women, remains one of the most common indications for prescribing antibiotics.[1,2] *Escherichia coli* is the most common pathogen, followed by *Klebsiella pneumoniae*, *Proteus mirabilis* and other *Enterobacteriaceae*. A wide range of antibiotics are prescribed, which impacts resistance rates.

Acute pyelonephritis with community onset is an ascending UTI involving the kidneys and may be associated with bacteraemia.[3] Although pyelonephritis is less common than cystitis, it causes important short-term morbidity and can lead to severe and sometimes fatal complications. The incidence is highest among young women, followed by infants and the elderly.[4] Similarly to cystitis, the most common pathogen is *E. coli* followed by other *Enterobacteriaceae*, with a wide range of variation. Acute pyelonephritis may be treated with oral antibiotics that cover the same spectrum of pathogens as cystitis, but it requires adequate antibiotic concentrations in the upper urinary tract and bloodstream.[5]

Antibiotic resistance

Community-acquired infections, including UTIs, caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, are becoming more common and pose a major healthcare burden and treatment challenge. ESBL-producing *Enterobacteriaceae* are commonly co-resistant to fluoroquinolones. Resistance data shows high rates of resistance to ampicillin, amoxicillin/clavulanic acid, oral cephalosporins, co-trimoxazole and ciprofloxacin in many countries. Resistance patterns of *E. coli* strains, the dominant uropathogen, vary considerably among regions and countries.[6]

Available treatment options

Increasing resistance rates have reduced oral treatment options. Oral fluoroquinolones are no longer recommended for empirical therapy of lower UTI in many countries, due to increased resistance rates and its potential for selection pressure and co-resistance to unrelated antibiotic classes. Oral fluoroquinolones may still be recommended for empirical treatment of acute pyelonephritis in countries with low resistance rates.

Nitrofurantoin, fosfomycin trometamol and pivmecillinam have been revived for treatment of cystitis (e.g. high-risk patients, long-term care facilities) because of high resistance rates to other antibiotics and to avoid the emergence of further resistance to commonly used antibiotics (e.g. fluoroquinolones). The above three antibiotics have proven efficacy against ESBL-producing *Enterobacteriaceae*, which might expand their use. However, they are not universally available and increased resistance rates can be anticipated following increasing use, particularly for fosfomycin trometamol and pivmecillinam.

Oral treatment options for pyelonephritis are even more limited, as many of the available treatment options are only suitable or approved for cystitis. Moreover, resistance to co-trimoxazole and fluoroquinolones severely affects treatment options for upper UTI caused by ESBL-producing *Enterobacteriaceae*.

Therapies in development

New oral drugs are being developed mainly for complicated UTI in hospitalized patients as follow-on oral treatment after a few days of intravenous (iv) treatment. Though several oral antibiotics are in clinical development, i.e. oral sulopenem (penem) and tebipenem (carbapenem), they are mainly modified compounds of old classes. Consequently, they may suffer from some class-specific cross-resistance or exert strong selection pressure if widely used in the community. There are a few agents in preclinical development, and the recent clinical failure of oral eravacycline calls for a target product profile (TPP) to guide the development of new oral antibiotic agents for UTIs.

Purpose of the TPPs

Cystitis: New oral antibacterial drugs without cross-resistance to existing classes and without selection pressure on existing classes are needed to provide an alternative to nitrofurantoin, fosfomycin trometamol and pivmecillinam. Such new drugs would require high urinary concentrations and activity, but not necessarily high blood concentrations.

Pyelonephritis: New oral antibacterial drugs and oral follow-on treatment after iv treatment in hospitalized patients without cross-resistance to existing classes and without selection pressure on existing classes are needed. Patients with infections involving the upper urinary tract require drugs with adequate blood and renal parenchyma concentrations and activity in urine.

Both: Ideally, any new medicine for lower or upper UTI would exert minimal collateral effects on human microbiota, inducing little selection pressure for emergence of resistance, particularly among gastrointestinal flora.

Access and affordability

- Access to new essential antibacterial treatments is an essential part of universal health coverage. Developers should commit to an access and stewardship strategy that promotes availability at fair prices. A fair price is one that is affordable for health systems and patients, but at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products.[7] To ensure access to patients in many countries, developers are invited to collaborate with the World Health Organization (WHO), the Global Antibiotic Research and Development Partnership (GARDP) and the Medicines Patent Pool where appropriate.

- Governments need to commit to ensure availability and affordability of essential new antibiotic treatments. In particular for reserve antibiotics,[8] governments should explore models where procurement and reimbursement are linked to availability instead of volume to foster appropriate use.
- Stewardship and appropriate use are essential to preserve the effectiveness of any new antibacterial treatment. Developers should not register the product for use in animals or plants or develop a treatment of the same class for use in animals or plants. The above-mentioned access and stewardship plan should be based on ethical promotion and distribution. Manufacturing should be in line with best industry practices in the management of emissions to the environment to minimize the risks of spreading AMR.

TPP for oral therapy of acute uncomplicated UTI (cystitis)

	Minimal TPP	Preferred TPP
Indication for use	Treatment of acute uncomplicated community-acquired lower UTI in women (cystitis).	Treatment of acute uncomplicated community-acquired lower UTI (cystitis) in women with confirmed or increased risk for multidrug-resistant (MDR) Gram-negative (incl. ESBL-producing) pathogens, or in need of an alternative therapy to nitrofurantoin, fosfomycin or pivmecillinam.
Target population	Adolescents and adults (women) with suspected MDR Gram-negative pathogens.	Adolescents and adults (women) with suspected MDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.	Comparable to current therapies with β-lactams, no indication for toxicity signals in preclinical reproduction toxicity studies.
In vitro activity	Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); low cross-resistance to known antibiotic classes (new class/target/ mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole, fosfomycin, nitrofurantoin; low propensity for mutational resistance development.	Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); no cross-resistance to known antibiotic classes (new class/new target/new mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.
Clinical efficacy	Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years).	Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years).
Formulation/ presentation	Suggestion: tablets/capsules/sachet	Suggestion: tablets/capsules/sachet
Dose regimen	1-3x daily, treatment duration 1-5 days	1-2x daily, treatment duration 1-5 days
Route of administration	Oral	Oral
Product stability and storage	Heat stable, 1-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).	Heat stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).
Pharmacokinetics	Pharmacokinetic data available to support use in lower UTI (renal elimination), activity in urine.	Pharmacokinetic data available to support use in lower UTI (adequate concentrations and activity in urine, potentially concentrations in blood).
Drug interactions	Comparable to current therapies	Comparable to current therapies

TPP for oral therapy of acute pyelonephritis

	Minimal TPP	Preferred TPP
Indication for use	Oral treatment or oral follow-on of iv treatment of acute pyelonephritis.	Oral treatment or oral follow-on of iv treatment of acute pyelonephritis, in patients with confirmed or at high risk of having MDR (incl. ESBL-producing) Gram-negative pathogens.
Target population	Adolescents and adults (men and women) with suspected MDR Gram-negative pathogens.	Adolescents and adults (men and women) with suspected MDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.
In vitro activity	Activity against Enterobacteriaceae (including *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); low cross-resistance to known antibiotic classes (new class/target/mode of action), especially to β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.	Activity against Enterobacteriaceae (including *E. coli*, *Klebsiella* and *Proteus* including ESBL-producers); no cross-resistance to known antibiotic classes (new class/target/mode of action), especially to β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.
Clinical efficacy	Non-inferior clinical activity in acute infections to currently used therapies against susceptible strains, e.g. aminoglycosides, cephalosporins and ciprofloxacin, carbapenems. Clinical trials should include elderly patients (> 65 years).	Non-inferior clinical activity in acute infections to currently used therapies against susceptible strains, e.g. aminoglycosides, cephalosporins and ciprofloxacin, carbapenems. Clinical trials should include elderly patients (> 65 years).
Formulation/ presentation	Tablets/capsules/sachet	Tablets/capsules/sachet
Dose regimen	1-3x daily, treatment duration 3-10 days	1-2x daily, treatment duration 3-10 days
Route of administration	Oral	Oral, or iv + oral
Product stability and storage	Heat stable, 1-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).	Heat stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).
Pharmacokinetics	Pharmacokinetic data available to support use in lower and upper UTI (adequate concentrations and activity in urine and blood).	Pharmacokinetic data available to support use in lower and upper UTI (adequate concentrations and activity in urine and blood).