TARGET PRODUCT PROFILE FOR THERAPY OF DIAGNOSED UNCOMPLICATED GONORRHOEA

World Health Organization

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Introduction

Disease burden

Gonococcal infection is the second most prevalent bacterial sexually transmitted infection (STI), and as such is a current public health problem worldwide.[1] *Neisseria gonorrhoeae* causes an estimated 87 million new cases annually, of which approximately half are asymptomatic. Symptomatic gonorrhoea results in urethritis in males and cervicitis in females. Untreated gonorrhoea can lead to epididymitis in males and pelvic inflammatory disease in females, which in turn can have serious sequelae such as infertility, ectopic pregnancy and chronic pelvic pain. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis, which may lead to scarring and blindness if untreated. Untreated gonorrhoea can also lead to disseminated infection with polyarthralgia, polyarthritis or oligoarthritis, and rarely to endocarditis. Finally, gonorrhoea can increase the risk of contracting and transmitting HIV and other STIs.[2] Gonorrhoea affects high-, middle- and low-income countries. The African region has the highest rates of gonococcal infection worldwide.[3]

Antibiotic resistance

Widespread antibiotic resistance in *N. gonorrhoeae* strains has increasingly compromised the management and control of gonorrhoea.[4] *N. gonorrhoeae* has evolved and acquired or developed resistance to all oral antimicrobials used for treatment – sulphonamides, penicillins, tetracyclines, macrolides and fluoroquinolones – leading to treatment failures. *N. gonorrhoeae* continues to show high rates of non-susceptibility to azithromycin in many countries, and the increasing emergence of strains with decreased susceptibility, and resistance to ceftriaxone is concerning.[5] Resistance to both agents of the dual therapy (ceftriaxone and azithromycin) and to other antibiotic classes (extensively drug resistant isolates) has emerged but is still rare.

Available treatment options

Currently, the empirical therapy for gonorrhoea in most countries is the injectable third-generation cephalosporin ceftriaxone and azithromycin. But high levels of resistance to both ceftriaxone and azithromycin have been reported. The recently released World Health Organization (WHO) treatment guidelines for gonorrhoea recommend dual therapy over monotherapy where resistance surveillance data is not available. In 2019 the US Centers for Disease Control and Prevention recommended dual therapy with a single dose of ceftriaxone given intramuscularly (im) plus oral azithromycin.[6] Because of increasing resistance to last-line treatment options, choices for antimicrobial treatment are becoming limited. Gentamicin is an option for treating ceftriaxone-resistant gonorrhoea, but it is not as effective as ceftriaxone.

Therapies in development

Because of the inherent risk of emergence of resistance of *N. gonorrhoeae* to antibiotics, continuous efforts to develop new treatments for gonorrhoea are inevitable. The target product profile (TPP) development will be essential to increase the pipeline of new treatments. The current clinical pipeline for gonorrhoea treatment is severely depleted due to lack of economic attractiveness and recent failures in Phase 3 clinical studies. Only two new antibiotics are in clinical development (zoliflodacin and gepotidacin), but several preclinical programmes target *N. gonorrhoeae*. WHO is now facilitating the development of a gonorrhoea vaccine after a successful proof-of-concept trial with meningococcal group B vaccine, but it is still in the early phase of development. Drug-drug interactions (DDIs) must be considered in patients on HIV treatment, as CYP3A4 can be induced by HIV protease inhibitors, and CYP3A4 metabolizes many medicines, including macrolides.

Purpose of the TPP

An initial TPP for gonorrhoea was developed by WHO and the Global Antibiotic Research and Development Partnership (GARDP).[7] This TPP is hereby being updated to ensure realistic expectations following the new WHO standardized methodology for developing TPPs. Co-infections with chlamydia are not addressed by this TPP. The minimal and the preferred TPP correspond to empirical and targeted treatment, respectively.

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.[8] To ensure access to patients in many countries, developers are invited to collaborate with WHO, 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,[9] 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 antimicrobial resistance (AMR).

TPP for therapy of diagnosed uncomplicated gonorrhoea

	Minimal TPP	Preferred TPP
Indication for use	Treatment of suspected or diagnosed uncomplicated urogenital gonorrhoea.	Treatment of diagnosed uncomplicated urogenital gonorrhoea and extra-genital gonorrhoea (anorectal and oropharyngeal).
Target population	Adults and adolescents in areas with resistance to the current recommended first-line treatment.	Adults and adolescents in areas with resistance to the current recommended first-line treatment.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For im use, good local tolerance.	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For im use, good local tolerance. Acceptable for use in pregnancy and lactation based on nonclinical studies.
In vitro activity	In vitro activity against *N. gonorrhoeae* resistant to extended-spectrum cephalosporins and macrolides, no cross-resistance to any other known antibiotic class (best achieved by a new class and/or new target and/or new mode of action). Activity measured by minimum inhibitory concentration (MIC) and dynamic in vitro models that account for protein binding, intracellular penetration and activity against intracellular bacteria. Low potential for emergence of mutational resistance.	In vitro activity against *N. gonorrhoeae* resistant to extended-spectrum cephalosporins and macrolides, no cross-resistance to any other known antibiotic class (best achieved by a new class and/or new target and/or new mode of action). Activity measured by MIC and dynamic in vitro models that account for protein binding, intracellular penetration and activity against intracellular bacteria. Low potential for emergence of mutational resistance.
Clinical efficacy	Non-inferiority in clinical trials versus current standard of care, as in US Food and Drug Administration (FDA) guidance, for urogenital gonorrhoea.	Non-inferiority to current standard of care (as in FDA guidance) for urogenital gonorrhoea, and equivalent to current care for extra-genital gonorrhoea.
Dose regimen	1–3 doses, up to 3 days	Single dose preferred at least for urogenital gonorrhoea; but 1–3 doses, up to 3 days, acceptable to treat extra-genital gonorrhoea.
Route of administration	Oral or im	Oral or im
Product stability and storage	Heat stable, 3-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 acute infection.	Pharmacokinetic data available to support use in acute infection and elimination of colonizing extragenital bacteria and show intracellular activity.
Drug interactions	Minimal relevant DDIs, including HIV medicines and other STI treatments.	No relevant DDIs, including HIV medicines and other STI treatments.

Important documents

WHO guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/246114/9789241549691-eng.pdf?sequence=1, accessed 2 February 2020).

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