Draft Target Product Profile for a paediatric formulation of Azithromycin

Version 0.1 draft for public consultation, 15 October 2024

Introduction

Azithromycin is amongst the top ten prescribed antibiotics (IQVIA-MIDAS data). Among all macrolides, it provides advantages with a long half-life and once a day short regimens. Infections with macrolide sensitive organisms are currently nearly all treated with azithromycin. It remains a drug that is widely available and relatively inexpensive including in LMICs. Azithromycin has been identified as a priority antibiotic due to its utility in a wide range of disease indications with short duration treatments, wide availability and low adverse event profile.

Indication

Azithromycin is the first choice drug for cholera, enteric fever, gonorrhoea, sexually transmitted infection due to chlamydia trachomatis, trachoma, yaws and chlamydia ophthalmia in the WHO AWARE Book (1,2). It remains one of the few choices for treatment of pertussis. Evidence of its utility in acute dysentery, atypical pneumonia (in countries where resistance has not yet developed), lower respiratory infections, scrub typhus and as an alternative to amoxicillin and amoxiclav was presented. The TPP development group concluded that evidence supported the treatment of enteric fever, cholera, acute dysentery, yaws, trachoma, scrub typhus, pertussis and atypical pneumonia in children.

Assessment of existing formulations

In the case of azithromycin, previously listed formulations, such as capsules, were found to be inappropriate for young children due to limited dose flexibility and patient acceptability issues. Although a powder for oral liquid formulation exists, it posed challenges like excipient safety and reconstitution requirements, which were considered problematic in low- and middle-income settings. A need for an age-appropriate oral formulation of azithromycin that includes safer excipients and does not require reconstitution was identified. This comprehensive approach aims to ensure that the Essential Medicines List for children includes formulations that are truly suitable for paediatric use, addressing both technical and practical challenges faced in diverse healthcare settings. Existing dispersible preparations in India underscored the potential for dispersible tablets provided they met stringent the more regulatory environments in the West and Europe.

Optimize Dosing

Optimal dosing for various indications of azithromycin ranged from 10 mg to 20 mg per kg of body weight. Single scoring was identified as the easiest form to break for usage, without long storage of the remaining pieces. Various dispersible tablet sizes of 60 mg, 80 mg, 100 mg and

120 mg were considered and modelled in terms of number of tablets and or fractions would be required to provide appropriate dosing across age groups. A single formulation at 60 mg would require 5 tablets for children at 15 kg or above. The group concluded that availability of scored tablets sized at 100 or 120 mg would reduce the number of tablets larger children would have to ingest while also being compatible with weight band dosing. Nevertheless, if dispersible scored tablets are not available, 50 mg dispersible tablets or dispersible multi particulates should be considered.

Formulation considerations

Indications for Azithromycin use included uses very early in life as well as for older children. Therefore, the group identified the need for formulations that would be required to accommodate infants and children who would be incapable of swallowing tablets without compromising shelf life and other logistic considerations (transport, ease of storage etc.). Dispersible multiparticulates (sprinkles, minitabs, granules etc.), nasal formulations were considered in addition to dispersible tablets; issues of volume restrictions for nasal and oral films limited their breadth of age-dosing combinations. Given the issues of syrups with transport, storage and shelf life, scored dispersible tablets were determined to be the minimum desirable formulations with dispersible scored tablets and affordable multiparticulates were considered optimum formulations. The need for scoring to be precise and functional so that the same amount of active ingredient would be available in each broken piece was stressed for azithromycin and all antibiotics being discussed. Double scoring of brittle dispersible tablets was also considered difficult while maintaining functionally precise breakage.

Access and affordability

Access to new, essential antibacterial treatments is a crucial component of universal health coverage. Developers should adhere to an access and stewardship strategy that ensures paediatric formulations of antibacterial are available at fair prices. To facilitate access for patients in various countries, developers are encouraged to collaborate with the WHO and GAP-f partners where appropriate.

Stewardship and appropriate use are critical for maintaining the effectiveness of new antibacterial treatments. Developers should refrain from registering these products for use in animals or plants or from creating similar treatments for such use. The access and stewardship plan should be grounded in ethical promotion and distribution practices. Additionally, manufacturing should adhere to best industry practices for managing environmental emissions to reduce the risk of spreading antimicrobial resistance.

Aim

This target product profile (TPP) aims to inform regulatory authorities, manufacturers, health programs, and other stakeholders about the need to develop optimal age-appropriate formulations of azithromycin.

For each characteristic of the TPP, product developers should aim to meet a preferred criterion whenever possible, with a minimal criterion as a fallback if the preferred one is not feasible. In cases where the two columns are combined, the preferred and minimal criteria are identical.

World Health Organization

GAP·f Global Accelerator for Paediatric formulations WHO Hosted Network

Target Product Profile summary

Characteristic	Description	Preferred target product profile	Minimum target product profile
Indication for use (compulsory)	For which purpose is the product to be used according to WHO guidelines and/or recommendations?	Chlamydial Ophthalmia, Trachoma, Cholera, Dysentery, Enteric fever, Pertussis, Yaws, Scrub typhus, Atypical Pneumonia	Trachoma, Cholera, Yaws, Pertussis, Enteric fever
Target population (compulsory)	Which age and weight bands should be targeted for using the product	From birth (including LBW and pre-term) to 25 kg	From birth to 25 kg
Safety	Is the product safe and tolerated? Are there excipients that are well known to be safe in children?	API safety is extrapolated from bioequivalence. Excipients selected in accordance with regulatory guidelines on inactive ingredients(3)	
Efficacy	What is the demonstrable or anticipated efficacy? Is matching adult exposure resulting from the administration of the dosage form equivalent to reference product?	Demonstrated bioequivalence to reference product	
Pharmaceutical form	What is the preferred type of pharmaceutical form to be developed?	(Functionally) Scored dispersible tablets or dispersible multiparticulates	(Functionally) Scored dispersible tablets
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	100 mg scored	50 mg
Weight based Dosing*	Is the dosage form compatible with WHO weight-band dosing?	Possible to administer the same dosage form across multiple weight bands	
Size of the dosage form	How big is the dosage form? Can it	Formulation should require minimum amount of liquid to form a homogenous dispersion for administration	

	be swallowed by young children? What is the volume of liquid to administer the formulation (i.e. DT)		
Acceptability and palatability	How is palatability? Are taste and texture acceptable and palatable for children?	Palatable, child-friendly flavour, good mouth feel demonstrated by an acceptability study	Palatable, acceptable taste and mouth feel with use of excipients, particularly flavours & sweeteners, commonly used in paediatric formulations.
Administration considerations	Are there specific requirements or considerations for the administration of the product? Are there clear administration instructions for caregivers?	Easy to administer – minimum manipulation by the caregiver. Minimal opportunity for child to reject medication Solid oral dosage forms Preferred. If bottle pack, then it should have a child-resistant cap	Solid oral dosage forms Preferred. If bottle pack, then it should have a child-resistant cap
Administration device consideration	Is there a need for an administration device? Are instructions needed?	No device needed	Minimum instructions necessary to use device if needed (dosing cup, spoon etc)
Preparation before administration	Is any preparation before administration required? If so are there clear and easy to apply instructions? Is it easy to prepare in all settings? Is clean water required?	Should not require complex preparation by the end-user before administration. Easy to prepare and administer, such as with water, milk or food. Clear instruction suitable for low-literacy settings	Easy to prepare and administer, such as with water, milk or food. Clear instructions suitable for low-literacy settings

Stability and storage requirements	What should be the optimal stability and storage requirements of the product? Should the formulation be heat/humidity stable? how long should be an acceptable shelf life before use and 'in-use'? Are there cold chain requirements?	Suitable for all climatic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and ≥24 months total shelf life No special transport and storage handling requirements No cold chain requirements	Suitable for the supply chain and end-user. No special transport and storage handling requirements or easy to transport and store No cold chain requirements
Packaging	What should be the preferred packaging for the new product?	Compact, lightweight, easy to open and administer, inexpensive, easy and low cost to transport, sustainable packaging. Child proof packaging	
Cost	What should the cost of the new product be?	Compared to existing formulations, no additional-cost (total cost of goods and landed costs) acceptable/affordable to caregivers, program managers and funders	Compared to existing formulations minimum additional-cost (total cost of goods and landed costs) but acceptable/affordable to caregivers, program managers and funders
Regulatory	Is the regulatory pathway clear? Should there be plans for registration in countries with population in need?	Plan for registration pathway(s), considering opportunities for good reliance practices, aiming for global registration as much as possible	Plan for regulatory pathways in end-user countries considered up front
Disability Requirements for Name on Product Label		For example, Braille labelling or "talking patient information"	Due consideration for end-user disabilities

References

1. The WHO AWaRe (access, watch, reserve) antibiotic book. Available from: https://www.who.int/publications-detail-redirect/9789240062382. Retrieved 26 Sep 2024.
2. Web Annex B. World Health Organization Model List of Essential Medicines for Children – 9th List, 2023. In: The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24 – 28 April 2023. Geneva: World Health Organization; 2023 (WHO/MHP/HPS/EML/2023.03).
3. WHO guidelines International Pharmacopeia National reg guidelines, Available from: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia.