Draft Target Product Profile for a paediatric formulation of Hydroxyurea

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Introduction

Hydroxyurea (HU) also known as hydroxycarbamide, is an oral antineoplastic drug and an inhibitor of ribonucleotide reductase that has shown to have many beneficial effects for treating sickle cell disease (SCD).[1] These effects include increasing foetal haemoglobin (HbF) concentration in RBCs, improving metabolism of nitric oxide, and reducing red cell-endothelial interaction and erythrocyte density.[2,3] These disease-modifying effects have been shown to decrease episodes of pain, acute chest syndrome, hospital admissions and the need for transfusions.[4,5] In high-income countries, HU is the first line primary disease modifying therapy for patients with SCD regardless of clinical severity. Its efficacy and effectiveness in children and adults with SCD have also been shown in low resources settings. [6,7]

The availability of hydroxyurea is still limited in low- and middle-income countries, particularly in Sub Saharan Africa, where 50-90% of children with SCD still die before the age of 5 years because interventions to manage and treat SCD, including treatment with hydroxyurea, are not currently provided as a standard of care or are mostly inaccessible to patients.[8]

Indication

WHO is finalizing guidelines on the management of SCD in children and adolescents, which include a strong recommendations for the use of HU in individuals aged 9 months to 19 years with sickle cell anaemia (SCA) regardless of clinical severity. Evidence demonstrates that HU significantly reduces the frequency of acute chest syndrome, dactylitis, painful crisis and hospitalizations. To reflect the genotypes with the strongest evidence for hydroxyurea efficacy, the group agreed that both the preferred and minimum target product profile should specify the indication as children and adolescents with sickle cell anaemia, specifically those with genotypes HbSS and HbSβ⁰-thalassaemia.

Consideration was given to specifying the appropriate service level for treatment initiation, particularly when considering preferred versus minimum targets for the intended population (e.g., initiation at primary versus referral level facilities, or by physicians versus other authorized prescribers). The group agreed that these choices largely fall under programmatic implementation. The aspirational goal of the programme remains to enable initiation of treatment for all children and adolescents with SCA (9 months–19 years) across all levels of the health system, as capacity and appropriate safeguards permit.

Assessment of existing formulations

Multiple formulations of hydroxyurea are currently available, including scored tablets, capsules and oral suspensions. The most widely available and utilized formulation is the 500 mg capsules. However, it presents dosing challenges in younger children, often requiring broad dose

approximations or alternative day administration. From an acceptability standpoint, capsules are unsuitable for younger children owing to swallowing issues. Alternative formulations such as 100 mg single-scored and 1000 mg triple scored film-coated tablets are available and registered in EU and allow for 50 mg and 250 mg dose increments, respectively. Despite their dosing flexibility, these tablets are not labeled as fully dispersible and have limited availability in low- and middle-income countries. For children or patients unable to swallow tablets, these can be disintegrated in water immediately before use, although this is not their intended use.

In some African countries, 100 mg and 250 mg capsules are registered and can be opened and mixed with food or liquids. While some are reported to have acceptable taste profile comprehensive data on their palatability remain limited. Oral suspensions are available in select markets but pose significant challenges in LMICs due to excipient safety concerns, bulky packaging (often glass containers), and short shelf life once opened. These factors limit their feasibility for widespread use.

Given these constraints, the group emphasized the need to reach consensus on age-appropriate HU formulation(s) to guide development, manufacturing and implementation. This would streamline procurement and improve access, particularly in resource-limited settings.

Optimize Dosing

Dosing strategies for HU vary across settings. Lower doses (e.g. 10 mg/kg) have been investigated and are currently being used in India,[9,10] demonstrating good safety profile and minimal need for intensive monitoring. In contrast, maximum tolerated doses (also referred to as optimal therapeutic doses) aim to achieve the highest dose without compromising safety, typically ranging between 30-35 mg/kg. Due to HU dose-dependent toxicity, doses above 35 mg/kg are not typically recommended.

Given that higher doses typically require substantial monitoring, many national guidelines recommend initiating at a fixed dose of 15 - 20 mg/kg, with the option to escalate based on stability and laboratory parameters.

Several ongoing trials in East and West Africa are exploring different dosing strategies. Most are using a starting dose of 20 mg/kg, while others evaluating lower doses, notably between 10 and 20 mg/kg including fixed-dose and dose-escalation approaches.[11]

Formulations considerations

Hydroxyurea is indicated for use from early infancy through to adolescence, including in children with non-severe disease. Consequently, the group emphasized the need for age-appropriate formulations that can be safely and effectively administered to infants and young children who may be unable to swallow tablets. Due to the logistical challenges associated with syrups, such as bulkiness, transport, storage, and limited shelf life once opened, scored dispersible tablets were identified as the most desirable formulations. This preference applies to both minimum and optimal product profiles, given their practicality, ease of administration, and adaptability across age groups. The group emphasized that tablet scoring must be precise and functional, ensuring that each subdivided portion contains an equal amount of active pharmaceutical ingredient. To minimize waste, any unused broken tablets can be safely stored in the original container and used within a three month period.

No concerns were raised regarding toxicity of the active pharmaceutical ingredient during handling or scoring. While triple scoring is uncommon in pharmaceutical development, the availability of triple-scored hydroxyurea tablets reassured the group that such an approach is feasible. It was also noted, however, that currently available hydroxyurea formulations with triple scoring are not marketed in dispersible tablet form. Given the particularly bitter taste of the active pharmaceutical ingredient, the group stressed the need to develop taste-masked formulations, thus improving palatability irrespective of whether they are swallowed whole or administered after dispersing in water.

Recognizing the complexity of implementing maximum therapeutic dose strategies, which often require dose escalation and close monitoring, the group identified the availability of both 50 mg and 250 mg dose increments as a priority. To support this, the development of 1000 mg triple-scored and 100 mg single-scored dispersible tablets was considered optimal, as these formulations would also facilitate administration in younger children who cannot swallow tablets. However, given the anticipated slow uptake of paediatric hydroxyurea and anticipated market dynamics that may initially limit the viability of multiple formulations, a 500 mg scored tablet was identified as a minimum acceptable dosage form to enable treatment.

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 hydroxyurea for use in children.

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.

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?	Sickle cell anaemia (HbSS and HbSβ⁰-thalassemia) of any clinical severity, with an effect on including recurrent vaso-occlusive crises, acute chest syndrome, stroke and other severe complications	
Target population (compulsory)	Which age and weight bands should be targeted for using the product	From 9 months to 19 years of age	
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 (if not eligible for a BCS biowaiver). Excipients selected in accordance with regulatory guidelines on inactive ingredients	
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 if not eligible for a BCS biowaiver	
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	1000 mg (triple scored) 100 mg single scored	500 mg single scored
Pharmaceutical form	What is the preferred type of pharmaceutical form to be developed?	(Functionally) Scored dispersible tablets. Taste masking is critical to improve adherence	

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 be swallowed by young children? What is the volume of liquid to administer the formulation (i.e. DT)	Formulation should require minimum amount of liquid to form a homogenous dispersion for administration; tablet size should not lead to acceptability issues for older children who are given the tablet whole.	
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, packed in aluminum blister packs.	Solid oral dosage forms preferred, packed in aluminum blister packs. 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
Service delivery level	At which level of the healthcare system should treatment be delivered?	Initiation at all levels of care including PHC with appropriate safeguards.	Initiation at secondary or referral level by trained clinicians. Maintenance at all levels of care including PHC with appropriate safeguards
Stability and storage requirements	What should be the optimal stability and storage requirements of the product? Should the formulation be heat/humidity	Suitable for all climatic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and ≥24 months total shelf life	Suitable for the supply chain and end-user. No special transport and storage handling requirements or easy to transport and store No cold chain

	stable? how long should be an acceptable shelf life before use and 'in-use'? Are there cold chain	No special transport and storage handling requirements No cold chain requirements	requirements

	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 SRA/WLA approved formulations, no additional-cost (total cost of goods and landed costs); acceptable/affordable to caregivers, program managers and funders	Compared to existing SRA/WLA approved 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

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