Target Product Profile for a paediatric formulation of mercaptopurine (6MP)

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Introduction

Mercaptopurine (6MP) is a thiopurine-derivative antimetabolite that blocks the formation of purine nucleotides and inhibits DNA synthesis, when incorporated into the DNA, it disrupts DNA replication (1-3). Mercaptopurine was identified as a priority cancer medicine since it is used as frontline therapy and an essential component in treatment plans for a number of childhood cancers. Mercaptopurine was flagged as there was a highlighted opportunity to improve the existing liquid formulation to a preservative free form which would increase the shelf life, and there is limited access to this formulation in low and middle –income countries (LMICs) (5). Developing a more easily titratable non-liquid oral dosage formulation would allow for safer administration in paediatric patients (5).

Indication

Mercaptopurine is used as frontline treatment and is an essential component in the treatment plans of acute lymphoblastic leukaemia (ALL), acute promyelocytic leukaemia (APL), lymphoblastic lymphoma, anaplastic large cell lymphoma and Langerhans cell histiocytosis (LCH) as listed on the WHO Essential Medicines List for Children (EMLc) (4). Mercaptopurine can also be used in relapse / refractory settings for the listed indications. In the treatment of ALL and LCH mercaptopurine has been used in certain settings as early as at 1 month of age.

Assessment of existing formulations

The existing mercaptopurine 50 mg tablet was noted to have limited dose flexibility and acceptability for younger children. Children 0-5 years of age were noted to have difficulty in swallowing the tablet (round 10 mm). There was an oral liquid (20 mg/mL) formulation also available but contains several excipients of concern, is packed in glass bottles to protect from moisture, and only has an 18-month shelf life. The oral suspension of mercaptopurine can be costly and only found in some markets with regulatory barriers in other markets. There is also an oral liquid extemporaneous fast dissolving 10 mg formulation under development. In resource limited settings given access issues it is more common to crush the tablets or give alternate day of week schedules. The recommendation was to develop an age-appropriate formulation with superior excipient safety and stability as compared to the oral liquid.

Optimize Dosing

The 10 mg scored in a dispersible tablet form would be the optimal dose unit that would be acceptable for younger patients and cover the infant stage. This formulation would allow for dose range flexibility for target population and better swallowability. The dose range typically for mercaptopurine is 25-75 mg/m^2 and can be given daily in 7-to-84-day cycles depending on the treatment plan or regimen. The target product profile (TPP) development group compared dispersible tables, minitablets, and multiparticulates evaluating multiple factors such as handling, taste, and swallowability. When scoring a tablet, it was taken into consideration that there is potential increased risk of exposure through inhalation of aerosols and drug particles, skin contact, or ingestion that could occur when the caregiver is administering the cytotoxic medications at home. The evidence and literature were reviewed and there were no concerns highlighted regarding the handling of mercaptopurine that flagged any serious concerns in scoring the medication.

Formulation considerations

Mercaptopurine (and its monohydrate salt) is a BCS Class II compound and has poor aqueous solubility and variable pharmacokinetic characteristics. Achieving bioequivalence to existing formulations will be challenging. Mercaptopurine reacts with strong oxidizing agents, and strong acids and bases. Mercaptopurine is likely to have a bitter taste so taste-masking via the use of flavours/sweeteners and/or coating will be required, depending on dosage form (coatings considered to be more effective). Dispersed dosage forms may also have a gritty texture. If taste masking or flavouring is not possible for the dispersible tablets the oral solution could also be given at the back of the throat to elicit the gag reflex so the child swallows. The dispersible tablets when added to a liquid would make a suspension so careful container rinsing would be needed and extra caution required in neonates and young infants in calculating total fluid volume. There would need to be additional education in handling provided to the caregiver to minimize risks of toxicity.

The handling of mercaptopurine should always be in accordance with current guidelines on safe handling of cytotoxic agents. Direct contact can cause local irritation and systemic absorption. Crushed or broken tablets may release airborne particles, posing inhalation hazards. Improper handling can lead to contamination of surfaces, increasing exposure risk to others. Use of gloves is recommended. Dosage forms that may generate aerosolized particles may have high risk of exposure; coating reduces risk of exposure. All handling and dose preparation activities for all dosage forms require the use of appropriate personal protective equipment (PPE).

Aim

This TPP aims to inform regulatory authorities, manufacturers, health programs, and other stakeholders about the need to develop optimal age-appropriate formulations of mercaptopurine.

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	Optimum or ideal 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?	Frontline and essential treatment for indications; can be used for relapse/ refractory treatment: acute lymphoblastic leukaemia (ALL), acute promyelocytic leukaemia, Lymphoblastic Lymphoma, Anaplastic Large Cell Lymphoma, and Langerhans cell histiocytosis (LCH)	Frontline and essential treatment for indications; can be used for relapse/ refractory treatment: acute lymphoblastic leukaemia (ALL), acute promyelocytic leukaemia, Lymphoblastic Lymphoma, Anaplastic Large Cell Lymphoma and Langerhans cell histiocytosis (LCH)
Target population (compulsory)	Which age and weight bands should be targeted for using the product	from birth	from 1 month old (consider LCH and ALL)
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	
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?	Scored dispersible tablets	Dispersible tablets
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	10 mg scored	10 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 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 To be dispersed in not more than 5-15 mL	
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 – Hand-washing before and after use with use of gloves if available Minimal opportunity for child to reject medication If bottle pack, then it should have a child-resistant cap	Easy to administer – Hand-washing before and after use with use of gloves if available 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, directly to the mouth or in water. Clear instructions suitable for low-literacy settings	Easy to prepare and administer, such as with water. 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. Mercaptopurine. USP Reference Standard 1392002. Darmstadt; Merck KGaA; 2024 (https://www.sigmaaldrich.com/US/en/product/usp/1392002 , accessed 1 July 2024).

2. Hageman L, Landier W, Hageman, Chen Y, Kim H, Kornegay N et al. Impact of 6 mercaptopurine (6MP) pill-taking habits on adherence, thioguanine nucleotide (TGN) levels and relapse risk in children with acute lymphoblastic leukemia (ALL): Results from a Children's Oncology Group (COG) study (AALL03N1). Blood. 2014; 124(21):369. doi. 10.1182/blood.V124.21.369.369.

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4. The selection and use of essential medicines 2023: web annex B: World Health Organization model list of essential medicines for children: 9th list. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/371091).

5. Paediatric drug optimization for cancer medicines: meeting report, 12th, 17th and 18th January 2024. Geneva: World Health Organization; 2024.