Target Product Profile for a paediatric formulation of methotrexate (PO/IT)

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Introduction

Methotrexate is a folate antagonist that is cytotoxic through inhibition of dihydrofolate reductase (DHFR), inhibition of thymidylate, and an alteration of the transport of reduced folates (1). This results in a decrease in DNA synthesis, repair and cellular replication (highly effective for rapidly dividing cells in the S phase of cell cycle) (1). Methotrexate (the per oral (PO) and intrathecal (IT) formulation) was identified as a priority cancer medicine as it has various indications of usage in childhood cancer for frontline, essential, relapse/refractory and palliative treatment modules (3). Methotrexate was flagged to develop a more age-appropriate formulation in a non-liquid oral dosage form (e.g. coated sprinkles, minitablets, dispersible tablets) that is more easily titratable (3). Consideration for improving the existing liquid formulation with excipients of concern to a preservative-free formulation with a longer shelf life would be more ideal in resource limited settings (3).

Indication

Methotrexate per oral (PO)/ intrathecal (IT) is used in frontline treatment and is an essential component in the treatment plans of acute lymphoblastic leukaemia (ALL), acute promyelocytic leukaemia (APL), anaplastic large cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma and Langerhans cell histiocytosis (LCH) (2). Methotrexate PO/IT can also be used in relapse / refractory settings as well as in palliative care treatment plans for the listed indications. The target product profile (TPP) development group was in agreement that osteosarcoma even though listed as an indication on the WHO Essential Medicines List for Children (EMLc) methotrexate PO was not commonly used in palliative treatment but is limited to metronomic therapy.

Assessment of existing formulations

Methotrexate is currently available in a 2.5 mg tablet formulation that was noted to have limited dose flexibility and acceptability for children. The oral liquid formulation (2-2.5 mg/mL) that is currently available (not on the EMLc) has limited availability in some settings, several excipients

of concern, a shorter shelf life with stability and storage requirements. The recommendation in prioritizing this medicine was to develop an age-appropriate formulation with superior excipient safety and stability as compared to the oral liquid formulation. A preservative-free formulation with a longer shelf life would be ideal in low- and middle-income country (LMIC) settings.

Optimize Dosing

The optimal unit dose of methotrexate would be a 2.5 mg orodispersible minitablets which would be suitable for current regimens in the paediatric populations that addresses the swallowability and need for precise dosing with a potential option of coating to mask the taste. The TPP development group discussed a number of dosage options and due to the risk of overdose and toxicity in younger populations the 2.5 mg tablet especially when dose adjusting during treatment plans would be a safer option. Caregivers are also used to the 2.5 mg dose and there would be less confusion in adapting a new formulation. The 2.5 mg dose was preferred over the 5 mg dose by the TPP development group for safety, ease of use, and less dose variability. The 2.5 mg dose also allows for precise incremental increases in dosage with less risk of error and would be safer as tablets would not have to be broken. There could be a high number of tablets in older children with a lower dosage form but since this will be disbursed in an appropriate amount of liquid this should not be a major concern. In older children the minitablets would be appropriate and having them disperse in a solution was address the taste and size issues with the formulation.

Formulation considerations

Methotrexate is a BCS class IV drug that is poorly soluble in water with low aqueous solubility and stability being PH dependent. The current crystalline forms of methotrexate are prone to physical instability so exploring alternative formulations could alleviate the physical instability. The oral absorption of methotrexate is dose dependent and can vary widely but generally is seen to have rapid absorption. The bioavailability of oral methotrexate is reduced by food, and particularly milk products. There is low and variable bioavailability, and the existing formulations could benefit from sweetener/flavour/coating as the current formulation is bitter. The preservative free IT methotrexate also has limited access in some areas. In the development of a new formulation the volume of dispersion should be considered as older children would require a higher number or tablets.

The handling of methotrexate (PO/IT) 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 methotrexate (PO/IT).

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, anaplastic large cell lymphoma, Burkitt lymphoma, lymphoblastic 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, anaplastic large cell lymphoma, Burkitt lymphoma, lymphoblastic 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
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?	Orodispersible minitablets	Dispersible tablets
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	2.5 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	Easy to prepare and administer, such as with water. Clear instructions suitable for low-literacy settings

		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. Methotrexate sodium. NCI Drug Dictionary. Bethesda: National Cancer Institute; 2023 ((https://www.cancer.gov/publications/dictionaries/cancer-drug/def/methotrexate-sodium , accessed 1 July 2024).

2. 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).

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