Target Product Profile for a paediatric formulation of cyclophosphamide

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Introduction

Cyclophosphamide is a cytotoxic nitrogen mustard derivative widely used in cancer chemotherapy that works by cross-linking genetic material in cancer cells, preventing DNA from uncoiling and replicating, thus preventing cell division (1, 2). At certain doses, cyclophosphamide can also enhance anti-tumour immune responses through T cell-mediated mechanisms. Cyclophosphamide was identified as a priority cancer medicine as it has a wide range of indications for childhood cancer and there is an opportunity to develop a formulation with reduced toxicity that is more easily titratable in a non-liquid oral dosage formulation at a lower strength which would potentially also allow for greater flexibility in procurement (4). Notably, cyclophosphamide capsules and tablets handling and manipulation by caregivers of patients can cause a risk of hazardous exposure. A child friendly formulation would be useful in low middle income countries (LMICs) where there is significant usage of cyclophosphamide in palliative and metronomic treatment plans.

Indication

Cyclophosphamide in the per oral (PO) formulation is typically used for palliative intent or immunosuppression in a wide range of cancers. The WHO Essential Medicines List for Children (EMLc) indications for all formulations of cyclophosphamide include acute lymphoblastic leukaemia (ALL), anaplastic large cell lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, low-grade glioma (LGG), Wilms tumour, and rhabdomyosarcoma (3). The TPP development group noted that oral cyclophosphamide is a component of metronomic regimens and relevant for central nervous system (CNS) tumours may be prevalent in LMICs; however, its use in LGG is uncommon. There are established standard of care uses for oral cyclophosphamide used as metronomic therapy for 6 months with rhabdomyosarcoma. In LMIC settings the oral cyclophosphamide would be valuable to consolidate up from treatment with more intensive chemotherapy as well as for some relapsed protocols for Rhabdomyosarcoma and Ewings sarcoma. The TPP development group also noted that we expand the indications to include other paediatric malignancies in which oral or other types of cyclophosphamide formulations could be used. Of note, there are also immunosuppressive properties outside of paediatric oncology that would expand usage and be beneficial in LMIC settings.

Assessment of existing formulations

Existing dosage forms of cyclophosphamide evaluated were tablets (25 mg, 50 mg) and capsules (25 mg, 50 mg). The tablet form was found to be inappropriate for young children due to limited dose flexibility. While exact dosing may depend on the diseases and specific protocol used, the weight-based dosing most commonly used for oncologic indications is 2.5 mg/kg once daily in 21–28-day intervals. Both tablet and capsule formulations should be swallowed whole without chewing; therefore, dose rounding must be used to achieve precise paediatric dosages. For children 0-5 years of age, it was noted that the poor acceptability was due to difficulty in swallowing the tablet (8 mm – 11 mm in size).

Optimize Dosing

The potential lowest unit dose of cyclophosphamide would be 10 mg as scored tablets which could be easily broken in half to the 5 mg dosage for usage in different settings. While scoring has its challenges with stability and handling of cytotoxic medication cyclophosphamide is a prodrug so in the inactive form the scoring would not be as concerning as per the evidence reviewed. The TPP development group discussed that the 5 mg unit dose would be the best minimum dosage form to ensure flexibility required by incremental dosage adjustments for more precise dosing. Dispersible tablets would provide greater flexibility to account for different regimens and the range in ages of patients addressing the swallowability and reducing cytotoxic handling concerns. If dispersible tablets are not feasible orodispersible minitablets in sachets would be acceptable.

Formulation considerations

Cyclophosphamide has been classified as Biopharmaceutics Classification System (BCS) Class I drug substance that can be administered orally with good bioavailability. Cyclophosphamide can be administered orally in different pharmaceutical forms, such as tablets, capsules and liquid preparations, with minimal changes in the pharmacokinetic profile. Of note, liquid formulations are not suitable due the inherent instability of cyclophosphamide in water. Cyclophosphamide can be dissolved in an organic solvent including polyol, propylene glycol, polyethylene glycol, glycerol or combinations of these.

Prolonged preparation time may lead to drug degradation if cyclophosphamide begins dissolving prematurely which could cause a loss of taste-masking effectiveness. If not prepared and administered immediately, multiparticulates may degrade, reducing efficacy or increasing impurity formation. The handling of cyclophosphamide 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).

Cyclophosphamide has a slight bitter taste that can be masked via the use of flavors/sweeteners and/or coating. Depending on dosage form coatings are considered to be more effective. The use of aqueous or solvent-based coating systems can lead to cyclophosphamide degradation or impurity formation. It is notable to avoid using acidic solvents or pH-altering excipients during coating processes to prevent degradation during manufacturing.The dispersed dosage forms may have a gritty texture. Cyclophosphamide is soluble so would not have a gritty texture after dispersion. However, the grittiness can still arise from insoluble excipients.

Cyclophosphamide's aqueous instability and sensitivity to impurities significantly influence formulation design. Low-risk options include dispersible tablets and orodispersible minitablets (in sachets). Oral dispersible films are promising but require careful handling of moisture sensitivity and multiparticulates are less favourable due to handling complexities

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 cyclophosphamide (PO).

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

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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?	typically used for palliative intent/immunosuppression: acute lymphoblastic leukaemia, anaplastic large cell lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, nephroblastoma (Wilms tumour), rhabdomyosarcoma, and other paediatric malignancies	typically used for palliative intent/immunosuppression: acute lymphoblastic leukaemia, anaplastic large cell lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, nephroblastoma (Wilms tumour), rhabdomyosarcoma
Target population (compulsory)	Which age and weight bands should be targeted for using the product	from birth	from 6 months 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?	(Functionally) Scored dispersible tablets	Dispersible tablets or orodispersible minitablets (in sachets)
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	10 mg scored	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 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. Cyclophosphamide. USP Reference Standard 1157002. Darmstadt; Merck KGaA; 2024 (https://www.sigmaaldrich.com/US/en/product/usp/1157002 , accessed 1 July 2024).

2. Cyclophosphamide. National Cancer Institute Drug Dictionary. Bethesda: National Cancer Institute; 2021 (https://www.cancer.gov/publications/dictionaries/cancer-drug/def/cyclophosphamide, accessed 1 July 2024).

3. 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).

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