Target Product Profile for a paediatric formulation of etoposide (PO)

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Introduction

Etoposide is a cytotoxic agent that is a semi-synthetic derivative of podophyllotoxin, which binds to topoisomerase II and ligates cleaved DNA molecules causing single- and double-stranded DNA breaks inhibiting DNA replication and transcription. It targets the G2 and S phases of the cell cycle, ultimately leading to apoptotic cell death (1,2). Etoposide was identified as a priority cancer medicine as it has a wide range of indications for childhood cancer and in oral form mainly for palliative treatment, and there is an opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage age-appropriate formulation (4). Notably, the capsules and tablets should not be manipulated by caregivers of patients due to risk of hazardous exposure. A child friendly formulation would be useful in low middle income countries (LMICs) where there is significant usage of etoposide in palliative treatments.

Indication

Etoposide in the oral formulation is typically used for palliative intent and in metronomic therapies for a wide range of childhood cancers notably in sarcomas and solid tumours. The WHO Essential Medicines List for Children (EMLc) indications for all formulations of etoposide include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), anaplastic large cell leukaemia, Burkitt lymphoma, Ewing sarcoma, Hodgkin lymphoma, Wilms tumour, osteosarcoma, ovarian germ cell tumour, retinoblastoma, and testicular germ cell tumours (3). The Target Product Profile (TPP) development group noted that Burkitt lymphoma and retinoblastoma were not notable common indications when using the oral etoposide formulation in practice and recommended expanding the indications of palliative intent to other paediatric malignancies that can use oral or other etoposide formulations.

Assessment of existing formulations

Previously listed formulations of etoposide in the capsule form were found to be inappropriate for young children due to limited dose flexibility and patient acceptability issues for the common dosage strengths in increments of 50 mg or 100 mg (4). There were some excipients of concern in the current formulation and the recommendation was to develop a formulation more suitable for children 0-5 years of age. The TPP development group discussed the current practice of using the oral injectable formulation for lower dosages and the challenges in administering high dosages that are required in paediatric protocols. Metronomic settings would benefit from a 25 mg lower dosage than currently available 50 mg even for adolescents or young adults.

The typical weight-based dosing for etoposide is 50 mg/m^2 that can be given daily in 21-day intervals. To account for this, alternate day-of-week schedules are often used to achieve an average daily dose (e.g. 50 mg MWF/100 mg TRSS), which can be challenging for caregivers and presents risks for error. An oral solution can be extemporaneously compounded from the intravenous formulation, but it requires challenging off-label, at-home dilution instructions (2).

Optimize Dosing

The potential lowest unit dose of etoposide would be a 10 mg dose and the TPP development group discussed that the 5 mg unit dose would be the minimum dosage form that is acceptable in various clinical scenarios to allow for more dose flexibility. When reviewed by the TPP development group orodispersible minitablets (1 – 3 mm granules/pellets) or coated multiparticulates (< 1 mm in sachets) were identified as the most acceptable (swallowable) pharmaceutical form. The volume of liquid needed for dispersion would be 5-15 mL of liquid (suspension produced – container rinsing may be required, care with total fluid volume) where children less than 6 months of age would need to take with a liquid while children over 6 months of age could ingest minitablets or multiparticulates with food.

Formulation considerations

Etoposide has been classified as BCS Class II drug substance that exhibits low-solubility and high permeability which can limit absorption. Oral administration of capsules containing a solution of etoposide in a solvent mixture has low and variable bioavailability that occurs from inactivation of the drug in gastrointestinal fluids and poses some challenges. Etoposide can be unstable in alkaline solutions and should be diluted and administered in neutral or slightly acidic solutions.

The solubility and permeability are the main concerns for solid oral dosage form. Making it soluble by changing the salt form or having another solvent similar to what is in the capsules are potential options that were discussed. The multiparticulates would have to be coated so they are not aerosolized and would address the low solubility and mitigates exposure concerns. When taste masking can be done by coating the minitablets the coating may be ruptured by chewing and/or dispersal in a vehicle. There would also likely be the need the using a counting device, unless dose banding is permitted e.g., via filling into sachets.

The handling of etoposide 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 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 etoposide (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.

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: acute lymphoblastic leukaemia, acute myeloid leukaemia, anaplastic large cell leukaemia, Ewing sarcoma, Hodgkin lymphoma, nephroblastoma (Wilms tumour), osteosarcoma, ovarian germ cell tumour, testicular germ cell tumour, and other paediatric malignancies	typically used for palliative intent: acute lymphoblastic leukaemia, acute myeloid leukaemia, anaplastic large cell leukaemia, Ewing sarcoma, Hodgkin lymphoma, nephroblastoma (Wilms tumour), osteosarcoma, ovarian germ cell tumour, testicular germ cell tumour
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?	Orodispersible minitablets or coated multiparticulates (in sachets)	
Unit dose	What is the quantity of active pharmaceutical	10 mg	5 mg

	ingredient delivered by the dosage form?		
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)	For minitabs 1-3 mm For multiparticulates <1mm in 5 ml of liquid If not possible to administer directly less than 5-15 ml of liquid should be used	
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. Etoposide. NCI Drug Dictionary. Bethesda: National Cancer Institute; 2019 (https://www.cancer.gov/publications/dictionaries/cancer-drug/def/etoposide, accessed 1 July 2024).

2. McLeod HL, Relling MV. Stability of etoposide solution for oral use. Am J Hosp Pharm. 1992; 49(11):2784–5. doi. 10.1007/s40268–014–0037–9

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.