Target Product Profile for a paediatric formulation of procarbazine

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Introduction

Procarbazine is a cytotoxic methylating agent with mutagenic activity, after metabolic activation it appears to inhibit the trans-methylation of methionine into transfer RNA (tRNA), thereby preventing protein synthesis disrupting DNA and RNA synthesis (1). Procarbazine was identified as a priority cancer medicine for its targeted indications and flagged for development due to the need of a lower strength for the paediatric population. There is an opportunity to reduce toxicity by developing a more easily titratable non-liquid oral formulation (minitablets, dispersible tablets) that would be more age appropriate and can be used in low resource treatment settings (3).

Indication

Procarbazine is a component of the treatment regimen for the listed indication of Hodgkin Lymphoma in the WHO Essential Medicines List for Children (EMLc) (3). It is also used in the treatment of central nervous system (CNS) tumours. It can be used in frontline treatment, depending on local standards of care, and can also be used in the relapse/refractory setting. The Target Product Profile (TPP) development group noted that procarbazine is more frequently used in practice for gliomas and medulloblastoma than for the EMLc listed indication of Hodgkin lymphoma has decreased over the years and been replaced by dacarbazine in some settings due to toxicity and access issues. In the case of Hodgkin lymphoma its use is now becoming very limited for this indication as it has been substituted for regimens with similar efficacy and less toxicity (OEPA-COPDAC). The regimen that still includes Procarbazine for the treatment of Hodgkins disease, BEACOPP has a significant relative risk of infertility more than 50% affecting more boys than girls. For the treatment of medulloblastoma it can be used in combination with lomustine and vincristine.

Assessment of existing formulations

The formulation is available in an oral 50 mg capsule that caters to adult dosage (typical paediatric dose 50–100 mg/m2 body surface area). There was noted limited dose flexibility and acceptability for children due to swallowability and having to sometimes split the dose in two.

The capsules contain mannitol which was flagged as an excipient of concern (2). The treatment of gliomas includes regimens that use a dosage range of 20-80 mg and sometimes the high doses can be challenging. Paediatric doses often require alternating schedules to achieve an average daily dose. There are directions from the manufacturer to extemporaneously compound an oral suspension; this suspension is only stable for seven days, but this may be acceptable for some regimens where procarbazine is given for seven days (or four doses). Use of this practice is limited by the ability to compound and ability of families to access and give the medicine within the appropriate time frame for stability.

Optimize Dosing

The optimal unit dose of procarbazine would be 20 mg as this would allow for dose flexibility and be a better option for the paediatric population. Dispersible tablets are considered for further investigation from the TPP development group as dose flexibility can be achieved by administering different numbers of dispersible tablets with caution of rinsing the vehicle used for dispersion. Minitablets may require a high number in older children.

Formulation considerations

Procarbazine is a BCS class I drug that has rapid and complete absorption and high solubility. Achieving bioequivalence to existing formulations is reasonable. It should be noted that excipients should not lead to degradation of procarbazine either in the tablet or in water and should not slow the dissolution thereof or reduce in any way the dissolving activity of the solubilizing agent. For palatability, there is a slight metallic taste that can be masked via the use of flavours/sweeteners and/or coating. Depending on dosage form coatings could be considered to be more effective and dispersed dosage forms may have a gritty texture. High solubility may exacerbate taste issues due to solubility in saliva. Prolonged preparation time may lead to drug degradation if procarbazine begins dissolving prematurely or loss of taste-masking effectiveness may occur. If not prepared and administered immediately, multiparticulates may degrade, reducing efficacy or increasing impurity formation.

The handling of procarbazine 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).

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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 procarbazine.

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.

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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?	Component of treatment; can be used as frontline (local standard of care) and relapse/refractory: gliomas, medulloblastoma	Component of treatment; can be used as frontline (local standard of care) and relapse/refractory: gliomas, medulloblastoma
Target population (compulsory)	Which age and weight bands should be targeted for using the product	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?	Scored dispersible tablets	Dispersible tablets
Unit dose	What is the quantity of active pharmaceutical ingredient delivered by the dosage form?	20 mg	10 mg

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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.
Administrationc onsiderations	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	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

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	settings? Is clean water required?	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

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References

1. Procarbazine hydrochloride. USP Reference Standard SML0036. Darmstadt; Merck KGaA; 2024 (https://www.sigmaaldrich.com/US/en/product/sigma/sml0036 , 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.

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