Drug – Target Product Profile (TPP)

Disease Area: Spontaneous preterm labour
Intervention/Candidate: Tocolytics

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This is a draft document and is undergoing public consultation. It is anticipated that the contents and structure of this document may change during this process

1 Introduction

BARRIERS TO IMPROVING MATERNAL HEALTH

An estimated 295,000 women die during pregnancy, childbirth and the postpartum period annually.(1) While this figure represents a 38% reduction in the maternal mortality ratio (MMR) since 2000, significant acceleration is needed in order to reach the Sustainable Development Goal 3 global target of 70 maternal deaths per 100,000 live births by 2030.(2) It is widely recognised that in order to improve global maternal and perinatal health, greater emphasis is needed on ensuring that effective, affordable interventions are much more widely available in low- and middle-income countries, but also that greater attention is needed on improving the quality of antenatal, intrapartum and postpartum care.(3-5)

Another significant barrier to progress in maternal health is under-investment in pharmaceutical research and development (R&D) of medicines for pregnancy-specific conditions.(6, 7) Many medicines that are regularly used for pregnant and postpartum women – such as methyldopa, beta-blockers, aspirin and nifedipine –were repurposed from other indications in non-pregnant adults. Their prescribing to pregnant women remains off-label in many countries despite strong evidence of benefit.(7) Developing innovative therapeutics that are effective, acceptable to women and providers, and easier to use could help address these implementation gaps. However, there is considerable under-investment in pharmaceutical R&D specific to obstetric conditions.

TARGET PRODUCT PROFILES

Target product profiles (TPPs) are a well-recognised strategy to promote development of innovative medical products, such as devices, diagnostic tests and therapeutics.(8-10) The World Health Organization (WHO) defines a TPP as a document that describes the minimum and preferred (or optimal) characteristics of a target product, aimed at a particular disease or diseases.(11) They specify the key characteristics that the intervention must address, such as (but not limited to) clinical indication, target population, desired efficacy, safety, formulation/presentation, stability and storage. TPPs identify upfront the characteristics a product should take, in order to fulfil a specific, unmet clinical and public health need.(10, 12)

TPPs are an important resource for multiple stakeholders in the R&D pathway, including funders, researchers, product developers, manufacturers and regulators.(10) TPPs can guide product developers on the operational characteristics that are required in order to meet end users' needs, and can help funders set specific targets. TPPs inform R&D strategies for researchers and manufacturers (including the design of clinical trials), help frame product dossiers and streamline communication with regulatory agencies.(13) Importantly, TPP development serves as a consensus-generating process, allowing key stakeholder groups to align around a clear set of product goals.(8) Importantly, medicines approved by the FDA that addressed a pre-specified TPP have been linked to more rapid regulatory review times.(14) This TPP has been developed in accordance with WHO's standard procedures for TPP development, and based on methods used in recently published TPPs.(8, 12, 15, 16)

PRETERM BIRTH

This TPP has been formulated to meet the need for novel treatments for spontaneous preterm labour. Spontaneous preterm labour accounts for up to 50% of preterm births. (17) Preterm birth is the leading cause of neonatal mortality, accounting for 35% of neonatal deaths globally. Preterm newborns that survive are at an increased risk of a number of short- and long-term adverse health outcomes, including chronic lung disease and neurological, visual and auditory disabilities.

Tocolytic agents are those that can slow down or stop the progression of labour. A number of tocolytic agents are currently in use internationally, which have been shown to prolong pregnancy for 2 to 7 days (18, 19), providing a window for administration of antenatal corticosteroids and/or in utero transfer of a woman to a higher level of care prior to birth. However, no tocolytic agent has been shown to improve substantive fetal or newborn health outcomes. There is an urgent need for new tocolytic agents that can prolong pregnancy and reduce the adverse perinatal outcomes associated with preterm birth.

2 Summary: Intervention Use Case

A therapeutic agent that can be administered by skilled health personnel to pregnant women experiencing spontaneous preterm labour, accompanied by monitoring of maternal and fetal well-being in antenatal care settings. The therapeutic agent will be safe for women and babies, facilitate prolongation of pregnancy and improve perinatal health outcomes.

Problem Definition: Preterm birth, defined as babies born alive before 37 completed weeks of gestation, is the leading cause of death in children under 5 globally; 35% of neonatal deaths are caused by preterm birth complications (20). Every year, nearly 15 million babies are born preterm, ~80% of which occur in Africa and South Asia (21). Neonates that survive preterm birth are at an increased risk of short- and long-term adverse health outcomes, including chronic lung disease, and neurological, visual and auditory disabilities. Up to 50% of preterm births are due to spontaneous preterm labour.(17) Although spontaneous preterm labour is one of the most common causes of hospitalization in pregnant women, the etiology and pathogenesis remain incompletely understood. Some tocolytic agents are available that can prolong pregnancy for 2 to 7 days, however there is a lack of evidence that current treatments improve substantive fetal and neonatal health outcomes. There is an urgent need for new tocolytics that can prolong pregnancy and reduce the adverse perinatal outcomes associated with preterm birth.
Target User Group: The beneficiaries will be pregnant women experiencing spontaneous preterm labour. The therapeutic agent will be primarily used by skilled health personnel working in antenatal care settings, caring for women in preterm labour. The therapeutic agent will benefit the

babies of women experiencing spontaneous preterm labour, by reducing the adverse perinatal outcomes associated with preterm birth.

Intended Use Case Scenario:
Use will be in pregnant women in spontaneous preterm labour, accompanied by monitoring of maternal and fetal well-being. The therapeutic agent will facilitate prolongation of pregnancy, allowing for further fetal maturation and administration of other therapeutics to improve fetal outcomes.

Medical Need:
Preterm birth is leading cause of death and disability in newborns. Globally, almost 15 million babies are born preterm every year, 40-50% of which are due to spontaneous preterm labour.

Tocolytic agents are those that can slow down or stop the progression of labour. A number of tocolytic agents are currently in use internationally, including calcium channel blockers (such as nifedpine), betamimetics (such as ritodrine) and oxytocin antagonists (such as atosiban). Some agents have been shown to prolong pregnancy for 2 to 7 days, which can provide a window for administration of antenatal corticosteroids and/or in utero transfer of a woman to a higher level of care prior to birth. However, no tocolytic agent has been shown to improve substantive fetal or newborn health outcomes. Current tocolytic agents in widespread use internationally (such as betamimetics and calcium channel blockers) also cause side effects that may lead to discontinuation.

Recent research suggests that the benefits of antenatal corticosteroids can be optimized when the time between administration and birth is increased (22) – this points to an increasingly important role for tocolytic administration to improve preterm newborn outcomes.

There is an urgent need for new tocolytic agents that can prolong pregnancy and reduce the adverse perinatal outcomes associated with preterm birth.

Executive Summary: TPP Core Variables

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Preferred *The preferred target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the **source data used and rationale** for why this feature is important.*
Indication	Treatment of women in spontaneous preterm labour	Same as minimum	A therapeutic agent intended to treat women in spontaneous preterm labour, to improve fetal and/or neonatal mortality and morbidity outcomes.
Target Population	Pregnant women up to <34 completed weeks of gestation experiencing spontaneous preterm labour	Same as minimum	The lower gestational age limit (i.e. fetal viability) varies between different settings. (21, 23) Tocolytic agents would be used for babies considered viable according to the relevant local definition.
Special Populations	Safe and effective across a range of gestational ages, including extremely preterm gestations. Safe and effective in pregnant adolescents.	Same as minimum	The lower gestational age limit (i.e. fetal viability) varies between different settings. (21, 23)
Population unlikely to be treated	Women in whom intrauterine fetal death has occurred or carrying a baby with a lethal fetal anomaly.	Same as minimum	Contraindications to a tocolytic agent are based on known contraindications to labour inhibition.(24)

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	Women in whom immediate delivery is indicated, such as women with eclampsia. Women with an intraamniotic infection or preterm prelabour rupture of membranes. Women with a contraindication to the tocolytic drug.		
Target Countries	All high, middle and low resource countries	Same as minimum	Approximately 15 million babies are born preterm globally, over 80% of which occur in Asia and sub-Saharan Africa. (17)
Clinical Efficacy	Clinically important difference in extending pregnancy duration to permit antenatal corticosteroid administration, in-utero transfer to higher level of care, and/or increase fetal maturity OR Clinically significant reduction in adverse fetal/neonatal outcomes associated with preterm birth, (such as neonatal mortality, respiratory distress syndrome, admission to the	Clinically important difference in extending pregnancy duration to permit antenatal corticosteroid administration, in-utero transfer to higher level of care, and/or increase fetal maturity AND Clinically significant reduction in adverse fetal/neonatal outcomes associated with preterm birth, (such as neonatal mortality, respiratory distress syndrome, admission to the NICU, or other preterm birth-related neonatal complications).	Clinical efficacy outcomes have been selected based on the core outcome set for evaluation of interventions to prevent preterm birth, the WHO recommendations on interventions to improve preterm birth outcomes and the primary outcomes in Cochrane reviews of tocolytic agents. (25)

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	NICU, or other preterm birth-related neonatal complications).		
Is a companion diagnostic needed for use?	No. Confirmation of preterm labour can be based on clinical examination.	Same as minimum	No specific tests are required, though in high-resource settings tests as such as fetal fibronectin are commonly used.
Need for clinical monitoring	Women in preterm labour require periodic clinical assessment (or monitoring) of maternal and fetal health and well-being. If drug side-effects are expected, additional monitoring for these may be required.	Women in preterm labour require periodic clinical assessment (or monitoring) of maternal and fetal health and well-being. No additional monitoring required for drug side-effects.	While undergoing tocolytic treatment, monitoring of maternal and fetal well-being may include monitoring of uterine contractions, cervical dilation, maternal blood pressure, temperature and urine production and fetal heart rate monitoring. Additional monitoring that may be required with administration of current tocolytics can include sonographic monitoring for oligohydramnios, and monitoring of maternal heart rate, glucose and potassium concentrations and renal functions.
Clinical Endpoint for Licensure	Clinically significant prolongation of pregnancy (time from trial entry to birth)	Clinically significant prolongation of pregnancy (time from trial entry to birth)	Clinical endpoints have been selected based on the core outcome set for evaluation of

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		Reduced incidence of adverse fetal/neonatal outcomes associated with preterm birth.	interventions to prevent preterm birth, the WHO recommendations on interventions to improve preterm birth outcomes and the primary outcomes in Cochrane reviews of current tocolytics.(25) Previous trials have demonstrated some tocolytics can provide 2 to 7 days prolongation. (18, 19)
Safety	Clinical safety (adverse or serious adverse effects for mother and baby) comparable to current therapies. Not contraindicated in pregnant and lactating women. Absence of fetal toxicity.	Fewer adverse effects than current therapies. No drug-related serious adverse events for mother or baby. Not contraindicated in pregnant and lactating women. Absence of fetal toxicity. No long-term adverse effects for mothers or babies.	Current tocolytic drug options include calcium channel blockers, oxytocin antagonists and betamimetics. Maternal side-effects of these drugs can include adverse injection site reaction, palpitations, chest-pain, hypotension, headache, hyperglycaemia, hypokalaemia, dyspnoea, nausea and vomiting, nasal stuffiness, flushing, and tachycardia. Maternal side-effects are more common in women taking betamimetics. (26)
Drug interactions	No significant drug-drug interactions with common antenatal	No drug-drug interactions with common antenatal	The tocolytic will be used alongside usual antenatal care.

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	treatments (medicines or supplements), or drugs used in women in preterm labour (antibiotics, corticosteroids).	treatments (medicines or supplements), or drugs used in women in preterm labour (antibiotics, corticosteroids).	Hence, the treatment must have minimal to no adverse interactions with drugs commonly used in pregnant women and women experiencing preterm labour.
Formulation Dosage & Administration	Non-invasive (including oral, inhaled or transdermal) or parenteral (including intramuscular, intravenous or infusion) Treatment regimen (dose and duration) dependent on clinical response to treatment.	Non-invasive administration (including oral, inhaled or transdermal) Treatment regimen (dose and duration) dependent on clinical response to treatment.	Non-invasive administration is preferred, as it would likely be more feasible and acceptable in low-resource settings, particularly in settings with limited capacity to administer and monitor women receiving infusions.
Treatment adherence	Frequency of discontinuation during therapy <20%	Frequency of discontinuation during therapy <10%	Large multi-centre trials of calcium channel blockers have reported discontinuation rates 5-20%. (19) Treatment adherence rates do not take into consideration access to healthcare services or supplies.
Stability / Shelf Life	Stable at 30°C Easy to transport and store. 2-year shelf life in climatic zone IVb	Stable at 30°C Easy to transport and store. 3 to 5-year shelf life in climatic zone IVb	Given the burden of preterm birth in LMICs, ease of transport and storage, as well as stability in hotter or humid

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	(simulated with 30°C and 75% relative humidity).	(simulated with 30°C and 75% relative humidity plus 6 month stability at 40°C and 75% relative humidity).	conditions is a priority.
Product Presentation	Easy to open and administer. Packaging must aim to protect and preserve the quality of the product and prevent damage to the drugs during transport and storage. *Injectable*: packaging must maintain sterility.	Compact, lightweight, easy to open and administer, sustainable packaging. Packaging must aim to protect and preserve the quality of the product and prevent damage to the drugs during transport and storage. Environmental impact of the packaging should be minimized	An easy to open and administer presentation will aid in the implementation of the novel treatment, as there will be minimal additional training requirements for healthcare workers.
Target Product Registration Pathway(s)	Approval by at least 1 stringent regulatory authority (e.g. US Food and Drug Administration, European Medicines Agency) Approval from relevant national regulatory authorities will also be required	Approval by at least 1 stringent regulatory authority (e.g. US Food and Drug Administration, European Medicines Agency) Approval from relevant national regulatory authorities will also be required WHO pre-qualification approval obtained	Use of a treatment in a given LMIC will require approval from their national regulatory authority. Product registration pathways are likely to differ for repurposed compared to novel drug treatments. Engaging with regulatory authorities early to discuss potential regulatory pathways, and streamline the

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			approval process is advised.
WHO Prequalification	WHO prequalification submission to be made within 12 months of Essential Medicines List (EML) inclusion.	Same as minimum	WHO PQ eligibility follows guideline and EML inclusion.
Primary Target Delivery Channel	*All:* Antenatal and childbirth care settings where women experiencing labour are managed and monitored. *Non-invasive administration:* Staff available to administer non-invasive treatment *Parenteral (including infusion):* Staff, supplies and equipment available and authorised to administer parenteral treatment	*All:* Antenatal and childbirth care settings where women experiencing labour are managed and monitored. *Non-invasive administration:* Staff available to administer non-invasive treatment	At a minimum, the treatment (non-invasive or parenteral) would be delivered in settings with the capacity to deliver that treatment and monitor maternal and fetal well-being.
Target Affordable Pricing / Procurement	Treatment is affordable in LMICs	Treatment affordable in the public sector in LMICs Unit cost of treatment is similar to other treatments for women experiencing spontaneous preterm labour	Given the burden of preterm birth in LMICs, affordability of any novel treatments is a high priority and an integral part of access planning.
Expected Financing Source	Procurement in LMICs financed by national governments, international agencies	Procurement financed by national	Procurement of medicines for use in pregnancy in LMICs varies between

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	(including UN organizations), and /or international donors, or private sector	governments or private sector	countries, but it may include governments as well as support from international organizations, agencies or funders. For a new treatment, initial support from international organizations or donors may be required. Procurement of effective treatments would ideally be prioritized by national governments.
Volume estimates	Volumes compatible with incidence of spontaneous preterm labour	Same as minimum	The estimated global incidence of preterm birth is 10.6%, equating to nearly 15 million preterm babies worldwide each year. (21) Global data suggests 21% of women in spontaneous preterm labour receive tocolytic drugs, though there it is likely many eligible women do not receive tocolytic treatment. (27)

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