Drug – Target Product Profile (TPP)

Disease Area: Pre-eclampsia
Intervention/Candidate: Drug treatment

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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 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, and 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.

1.1 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 and 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, therapeutics 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 standard procedures for TPP development and based on methods used in recently published TPPs. (8, 12, 15, 16)

1.2 Pre-eclampsia

This TPP has been formulated to meet the needs for novel therapeutic treatments for pre-eclampsia. Pre-eclampsia is the most common hypertensive disorder of pregnancy, affecting an estimated 4.6% of pregnant women globally, and is a leading cause of maternal mortality. (17, 18) The only cure for pre-eclampsia is delivery of the fetus and placenta, and there is currently a lack of effective medicines for treating pre-eclampsia. If pre-eclampsia is diagnosed at or near term, labour can be induced and delivery of the baby and the placenta can resolve the situation. However, if the diagnosis is made earlier, it is desirable to prolong the pregnancy so that the fetus can gain time to develop. Treatments (or temporizing interventions) to control, slow down or stop the disease process could therefore have a significant impact on survival and morbidity and mortality for the mother and the baby in both the short and long term.

2 Summary: Intervention Use Case

A therapeutic agent that can be administered by skilled health personnel to pregnant women diagnosed with pre-eclampsia of any severity, accompanied by monitoring of maternal and fetal well-being in antenatal care settings. The therapeutic agent will delay or prevent maternal disease progression, and ideally improve outcomes for the baby.

Problem Definition:
Hypertensive disorders of pregnancy are responsible for ~14% of maternal deaths globally, the vast majority (99%) of which occur in low and middle-income countries (LMICs) (18, 19). Pre-eclampsia and eclampsia account for the majority of maternal and fetal mortality due to hypertensive disorders of pregnancy. The International Classification of Diseases (ICD-11) describes pre-eclampsia as characterised by systolic blood pressure greater than 140mmHg or diastolic blood pressure greater than 90mmHg on two occasions, 4 hours or more apart in the presence of either proteinuria or other new onset maternal organ dysfunction, neurological conditions or fetal growth restriction.

The underlying aetiology of pre-eclampsia is incompletely understood; however, it involves abnormal placental development, imbalance in placental angiogenic factors and a pro-inflammatory response leading to uncontrolled maternal hypertension accompanied by either maternal organ failure (usually kidney or liver dysfunction), neurological symptoms and/or fetal growth restriction. The cure for pre-eclampsia is delivery of the fetus and placenta.

There is a currently a lack of effective medicines for treating women with pre-eclampsia and prolonging pregnancy.

Target User Group:
The beneficiaries will be pregnant women with pre-eclampsia and their babies. The therapeutic agent will be primarily used by skilled health personnel working in antenatal care settings, caring for women with pre-eclampsia.

Intended Use Case Scenario:
Use will be in pregnant women with pre-eclampsia of any severity, accompanied by monitoring of maternal and fetal symptoms in antenatal care settings. The therapeutic agent will will delay or prevent maternal disease progression, and ideally improve outcomes for the baby and the mother.

Medical Need:
Pre-eclampsia is a major cause of death and long-term disability in mothers and their babies, accounting for a quarter of maternal deaths in Latin America and a tenth of maternal deaths in Asia and Africa (20). The only cure available for pre-eclampsia is delivery of the fetus and placenta, however depending on gestational age, preterm delivery can increase the risk of neonatal morbidity and mortality. In women with severe pre-eclampsia, anti-hypertensive medicines are used to reduce the risk of severe maternal complications of hypertension including stroke and heart failure (21, 22). Magnesium sulfate is used to prevent the progression from pre-eclampsia to eclampsia (seizures) (23), however pre-eclampsia remains a significant burden to mothers and babies worldwide. There is an urgent need to identify new therapeutic agents to treat women with pre-eclampsia.

3 Executive Summary: TPP Core Variables

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Preferred *The preferred (or optimistic) target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations / Actual Product Performance[1] *For all parameters, include here the **source data used and rationale** for why this feature is important.*
Indication*	Treatment of women with suspected or confirmed pre-eclampsia, regardless of severity.	Same as minimum	A therapeutic target is intended to treat pre-eclampsia in pregnant women, and improve maternal, fetal and/or neonatal mortality and morbidity outcomes. Typically, more severe disease is associated with worse outcomes for mother and baby. Treatment initiated early in disease progression (e.g.: in women with mild disease) could potentially have greater benefits.
Target Population*	Pregnant women with suspected or confirmed pre-eclampsia, regardless of severity	Same as minimum	ICD-11 characterises pre-eclampsia as the new onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg) and proteinuria OR significant end-organ dysfunction after 20 weeks of gestation. As the resources for diagnosing pre-eclampsia may not always be available (particularly in low-resource settings), an agent that is effective in women with suspected pre-eclampsia would be more practical to implement across LMICs.
Special Populations	Safe and effective in pregnant women with pre-eclampsia, regardless of severity.	Safe and effective in all pregnant women with preeclampsia, including those diagnosed with HELLP syndrome or preeclampsia	The TPP for novel pre-eclampsia treatment is already targeting to a “special population” – pregnant women. The optimal requirements would deliver a safe and effective treatment for pre-eclampsia in all women,

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		superimposed upon chronic hypertension.	including those with HELLP syndrome or pre-eclampsia superimposed upon chronic hypertension, allowing for delivery of the intervention in settings where the accurate differentiation between pre-eclampsia subtype was not efficient.
Population/Segment unlikely to be treated	Women in whom immediate delivery is indicated (eg: eclamptic seizures, severe fetal growth restriction) Women with a non-viable pregnancy (eg: intrauterine fetal death has occurred). Women with a medical contraindication to the therapeutic agent.	Same as minimum	Pregnant women who require immediate delivery would be less likely to benefit from the treatment.
Target Countries	All high-, middle- and low-income countries	Same as minimum	The incidence of pre-eclampsia and eclampsia is estimated at 4.6% and 1.4% of pregnant women, respectively. (17)
Efficacy*	Clinically important difference in extending pregnancy duration to reach fetal maturity. OR Clinically significant reduction in serious adverse maternal outcomes associated with pre-eclampsia disease progression (such as mortality, severe-pre-eclampsia, eclampsia, stroke, etc.); OR	Clinically important difference in extending pregnancy duration to reach fetal maturity. AND Clinically significant reduction in serious adverse maternal outcomes associated with pre-eclampsia disease progression (such as mortality, severe-pre-eclampsia, eclampsia, stroke, etc.); AND	Efficacy outcomes have been selected based on priority outcomes in the WHO guidelines for treating women with pre-eclampsia, and the core outcome set for pre-eclampsia. (20, 24)

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	Clinically significant reduction in adverse neonatal outcomes associated with pre-eclampsia, (such as perinatal mortality, admission to the NICU, preterm birth or other pre-eclampsia-related neonatal complications).	Clinically significant reduction in adverse fetal/neonatal outcomes associated with pre-eclampsia, (such as perinatal mortality, admission to the NICU, preterm birth or other pre-eclampsia-related infant complications).	
Is companion diagnostic needed for use?	The International Classification of Diseases (ICD-11) describes pre-eclampsia as characterised by systolic blood pressure greater than 140mmHg or diastolic blood pressure greater than 90mmHg on two occasions, 4 hours or more apart in the presence of either proteinuria or other new onset maternal organ dysfunction, neurological conditions or fetal growth restriction. Proteinuria testing or special tests for organ dysfunction may be required for diagnosis.	Same as minimum	Special tests may be required for pre-eclampsia to be diagnosed. Proteinuria is diagnosed through urinalysis for protein in urine. Additional diagnostic tests include laboratory evaluation of platelet count, serum creatine and liver chemistries. (25) Other special tests (such as placental angiogenic factor-based testing) may be used for pre-eclampsia diagnosis in some settings. However, these are not widely available in LMICs.
Need for monitoring	Continued monitoring of maternal and fetal health and well-being until delivery.	Same as minimum.	Expectant management of women with pre-eclampsia includes regular monitoring of maternal blood pressure, as well as platelet count, serum creatinine and liver chemistries. Fetal growth and well-being also needs to be regularly assessed (20).
Clinical Endpoint for Licensure	Clinically important difference in extending	Same as minimum	Clinical endpoints have been selected based on priority

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	pregnancy duration to reach fetal maturity. Maternal clinical endpoints: death or major maternal morbidity (eclampsia, recurrent seizures, stroke, Pulmonary oedema, emergency caesarean, placental abruption etc.) Fetal/neonatal endpoints: death or major neonatal morbidity (respiratory distress syndrome birthweight, Intraventricular haemorrhage, NICU admission etc.)		outcomes in the WHO guidelines for treating women with pre-eclampsia, and the pre-eclampsia core outcome set. (20, 24)
Safety*	Clinical safety (adverse or serious adverse effects for mother and baby) comparable to current therapies. Not contraindicated in pregnant and lactating women. No suggestion of embryo-fetal toxicity or teratogenicity.	Fewer adverse effects than current therapies. No drug-related serious adverse events for mother or baby. Not contraindicated in pregnant and lactating women. No suggestion of embryo-fetal toxicity or teratogenicity.	Current treatments for specific manifestations of pre-eclampsia include antihypertensive drugs (e.g. methyldopa or labetalol) and magnesium sulfate. Drug options recommended by WHO for managing hypertensive disorders or pregnancy largely have acceptable safety profiles, though some lack evidence for fetal safety outcomes. (26, 27) Side effects of different anti-hypertensive drugs in pregnancy vary. For example, beta-blockers can cause oedema, postural hypotension, bradycardia, cold extremities, rashes, sweating, tachycardia, nausea, dyspepsia, vomiting and difficulty in micturition. (28) Common side-effects of methyldopa include dizziness, lightheadedness, drowsiness, headache, stuffy nose, and weakness, swelling, muscle pain, dry mouth, swollen tongue, gastrointestinal

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			symptoms and depressed mood. Side effects of magnesium sulfate include flushing, nausea and/or vomiting, slurred speech, muscle weakness, hypotension, dizziness, drowsiness or confusion, and headache. (23) This TPP is intended for a medicine that will interrupt the disease process and as such unlikely to be in any of the specific treatment categories mentioned above.
Drug interactions	Minimal drug-drug interactions with drugs used in women with pre-eclampsia (such as magnesium sulfate or tocolytics and corticosteroids for preterm labour)	No drug-drug interactions with drugs used in women with pre-eclampsia (such as magnesium sulfate or tocolytics and corticosteroids for preterm labour)	The treatment must have minimal to no adverse interactions with drugs commonly used in women with pre-eclampsia
Formulation Dosage & Administration	Oral (tablet) or parenteral (including intramuscular, intravenous or infusion) Treatment duration dependent on clinical response to treatment and severity of pre-eclampsia.	Oral (tablet) Treatment duration dependent on clinical response to treatment and severity of pre-eclampsia.	Current interventions for women with pre-eclampsia are delivered either orally or parenterally, as are experimental treatments being investigated for pre-eclampsia treatment in ongoing clinical trials.(21, 29) Oral 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 risks	Frequency of discontinuation during therapy <5%	Frequency of discontinuation during therapy <1%	Large multi-centre trials of magnesium sulfate and oral antihypertensives during pregnancy have reported

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			discontinuation rates of 1 to 3%. (30, 31)
Stability / Shelf Life	Cold-chain (2-8°C) requirement acceptable. Easy to transport and store.	Stable at 30°C Easy to transport and store. 2-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity).	Given the greater burden of pre-eclampsia in LMICs, ease of transport and storage, as well as stability in hotter or humid conditions is a priority. (18)
Product Presentation	Easy to open and administer. Packaging must aim to prevent damage to the drugs during transport and storage.	Compact, lightweight, easy to open and administer, sustainable packaging. Packaging must aim to 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. Packaging and design must comply with regulatory guidance from a stringent regulatory authority or WHO standards.
Target Product Registration Pathway(s)	Approval by at least 1 stringent regulatory authority (eg, 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 (eg, 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 approval process is advised.

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WHO Prequalification	WHO prequalification submission to be made within 12 months of Essential Medicines List (EML) inclusion.	Same as minimum	WHO PQ is a helpful step for registration in LMICs, who carry the greatest burden of pre-eclampsia. WHO PQ eligibility follows guideline and EML inclusion.
Primary Target Delivery Channel	*All:* Antenatal care settings where women with pre-eclampsia are managed and monitored. *Oral:* Staff available to administer oral treatment *Parenteral (including infusion):* Staff, supplies and equipment available to administer parenteral treatment	*All:* Antenatal care settings where women with pre-eclampsia are managed and monitored *Oral:* Staff available to administer oral treatment	At a minimum, the treatment (oral 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 with pre-eclampsia	Given the burden of pre-eclampsia in LMICs, affordability of any novel treatments is a high priority and an integral part of access planning. Current treatments for women with pre-eclampsia (antihypertensive drugs; magnesium sulfate) are generally widely available and affordable.
Expected Financing Source	Procurement in LMICs financed by national governments, international agencies (including UN organizations), and /or international donors, or private sector	Procurement financed by national governments or private sector	Procurement of medicines for use in pregnancy in LMICs varies between 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 maybe required.

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			Procurement of effective treatments would ideally be prioritized by national governments.
Volume estimates	Volumes compatible with current pre-eclampsia treatments	Volumes exceeding current pre-eclampsia treatments.	The estimated global incidence of pre-eclampsia is approximately 5%, equating to N=7 million women worldwide each year (though this may be an underestimate). (17) There are currently no reliable global estimates on the coverage of current pre-eclampsia treatments in pregnancy, though they are widely used.

3 References:

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