Drug – Target Product Profile (TPP)

Disease Area: Pre-eclampsia
Intervention/Candidate: Novel treatments for prevention of pre-eclampsia

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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 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. TPP's identify upfront the characteristics a product should take, in order to fulfil a specific, unmet clinical 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) In addition, 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 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 preventative therapeutics 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 a current lack of effective medicines for preventing pre-eclampsia.

2 Summary: Intervention Use Case

An affordable drug that can be administered to pregnant women identified as being at increased risk of developing pre-eclampsia. The drug will prevent the development of pre-eclampsia, have a good safety profile, can be commenced early in pregnancy (i.e. before 20 weeks' gestation) and can be continued throughout pregnancy, as required.

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 etiology of pre-eclampsia is incompletely understood, however it involves abnormal placental development, 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.

Despite the availability of some preventive treatments (such as low-dose aspirin for women at moderate or high risk of pre-eclampsia, and calcium supplementation for women with low calcium intake) many cases of pre-eclampsia are not prevented. An effective preventive agent for women at risk would therefore significantly benefit maternal and neonatal health globally.

Target User Group:
The beneficiaries will be pregnant women with identified moderate to high risk factors for pre-eclampsia and their babies. The preventive agent will be primarily used by skilled health personnel working in antenatal care settings, caring for women at risk of developing pre-eclampsia.

Intended Use Case Scenario:
Use will be in pregnant women identified as being at increased risk of developing pre-eclampsia, accompanied by monitoring for the development of pre-eclampsia in antenatal care settings. The drug will prevent the development of pre-eclampsia, have a good safety profile in pregnancy, can be commenced early in pregnancy (before 20 weeks' gestation) and can be continued throughout pregnancy as required.

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, however depending on gestational age, this can increase the risk of neonatal morbidity and mortality associated with preterm birth.

Women considered at high risk of pre-eclampsia include women with one or more of the following factors: diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal/neonatal death associated with pre-eclampsia. (21) Women are considered at moderate risk of pre-eclampsia if they have any 2 of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy. (21) In women identified as being at increased risk of developing pre-eclampsia, low-dose aspirin prophylaxis can reduce the frequency of pre-eclampsia and the related adverse maternal and fetal outcomes by 10-20%. (22) For women living in regions with low calcium intake, calcium supplementation can reduce the risk of developing pre-eclampsia (20). However, pre-eclampsia remains a leading cause of maternal and newborn morbidity and mortality globally. There is an urgent need to identify new agents to prevent pre-eclampsia.

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*	Prophylactic treatment of pregnant women at increased risk of developing pre-eclampsia	Same as minimum	The treatment is intended to prevent pre-eclampsia in pregnant women at increased risk, to improved maternal and fetal/neonatal mortality and morbidity outcomes.
Target Population*	Pregnant women with identified risk factors for pre-eclampsia	Same as minimum	While there is a lack of consensus on the criteria for identifying women at risk of pre-eclampsia, WHO recommendations on the use of antiplatelet agents for prevention of pre-eclampsia. (21) *moderate risk*: any two of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy; *high risk:* one or more of the following risk factors: diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal/neonatal death associated with pre-eclampsia. The recommendations note that this not an exhaustive list of factors for moderate- or high-risk stratification for pre-eclampsia, and can be adapted based on the local epidemiology of pre-eclampsia.
Special Populations	Safe and effective in individuals likely to experience common	Safe and effective in all pregnant women.	The population of women at increased risk of pre-eclampsia are also more likely to have other co-

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	drug-drug interactions (e.g. individuals with chronic hypertension, type I or II diabetes, chronic kidney disease or autoimmune disease).		morbidities, including chronic hypertension, type I or II diabetes, chronic kidney disease or autoimmune disease, which involve medication with a variety of drugs.
Population/Segment unlikely to be treated	Women with a medical contraindication to the preventive agent	Same as minimum.	
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) Approximately 16% of pregnant women in the UK are at an increased (moderate – high) risk of pre-eclampsia. (23)
Efficacy*	Clinically significant reduction in pre-eclampsia in women at increased risk.	Clinically significant reduction in pre-eclampsia in women at increased risk. Clinically significant reduction in serious adverse maternal or fetal/neonatal outcomes associated with pre-eclampsia	WHO recommends that women at moderate or high risk of pre-eclampsia be treated with low-dose aspirin as a preventative therapy. Based on evidence from 60 studies, aspirin probably reduces the risk of pre-eclampsia by 18% (RR 0.82, 95% CI 0.77 – 0.88). (21, 22)
Is companion diagnostic needed for use?	No. Identifying women at risk of pre-eclampsia requires a thorough history and clinical examination. Some conditions that increase risk of pre-eclampsia require use of special tests. *moderate risk*: any two of the following risk	Same as minimum.	A number of risk factors have been identified as increasing risk of pre-eclampsia (21) many of which are identified based on history and examination, though some (such as gestational diabetes or positive uterine artery Doppler) require special tests.

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	factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy; *high risk:* one or more of the following risk factors: diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal/neonatal death associated with pre-eclampsia.		
Need for monitoring?	Regular clinical assessments as part of standard care for women at risk of pre-eclampsia	Same as minimum.	Women at risk of pre-eclampsia should be regularly assessed in antenatal care settings to identify signs or symptoms of pre-eclampsia.
Clinical Endpoint for Licensure	Reduced incidence of pre-eclampsia amongst pregnant women at increased risk	Reduced incidence of pre-eclampsia Reduced incidence of adverse maternal and fetal/neonatal outcomes associated with pre-eclampsia.	Clinical endpoints have been selected based on primary outcomes in Cochrane reviews of current preventative treatments for preeclampsia, and priority outcomes used in WHO guidelines on preventing pre-eclampsia. (20, 22)
Safety*	Minimal clinical adverse effects for mother and baby. Not contraindicated in pregnant and lactating women.	No clinical adverse effects for mother and baby. No drug related serious adverse events.	

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	No suggestion of embryo-fetal toxicity or teratogenicity.	Not contraindicated in pregnant and lactating women. No suggestion of embryo-fetal toxicity or teratogenicity.	
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).	Preventive agent will be used alongside usual antenatal care for women at increased risk of pre-eclampsia. Hence, the treatment must have minimal to no adverse interactions with drugs commonly used in women with pre-eclampsia.
Formulation Dosage & Administration	Oral or injectable. Treatment can be commenced early in pregnancy (e.g.: prior to 20 weeks' gestation) and can be continued throughout pregnancy, as required.	Oral Treatment can be commenced early in pregnancy (eg: prior to 20 weeks' gestation) and can be continued throughout pregnancy, as required.	Current therapy is orally self-administered. Oral administration is preferred, and will promote acceptability, self-administration, and adherence in line with current therapies. Current novel technologies and therapies f or pre-eclampsia prevention include non-systemic, targeted, injectables. (24) Oral administration would likely be more feasible and acceptable for low-resource settings.
Treatment adherence risks	Frequency of discontinuation during therapy <20%	Frequency of discontinuation during therapy <10%	Large multi-centre trials of aspirin and calcium supplements during pregnancy have reported that high intake adherence rates (>80-90%) are required for improved health outcomes. Discontinuation rates are reported as <20%. (25, 26)
Stability / Shelf Life	Cold-chain (2-8C) requirement acceptable.	Stable at 30°C. Easy to transport and store.	Given the greater burden of pre-eclampsia in LMICs, ease of transport and storage, as well as

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	Easy to transport and store. 2-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity).	2-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity).	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. 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 treatment, as there will be minimal additional training requirements for healthcare workers or women to self-administer. 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 (e.g., 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., 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 Date	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 at risk of pre-eclampsia receive care. *Oral:* Staff available to provide and advise women on using oral treatment correctly *Injection:* Staff, supplies and equipment available to administer injectable treatment	*All:* Antenatal care settings where pregnant women are managed and monitored *Oral:* Staff available to provide and advise women on using oral treatment correctly	It is anticipated that the preventive agent will be used in antenatal care settings, particularly those where higher-risk women receive care.
Target Affordable Pricing / Procurement	Treatment is affordable in the public sector in LMICs	Treatment is affordable in the public sector in LMICs Unit cost of treatment is similar to other preventative therapies for women at increased risk of pre-eclampsia	Given the burden of pre-eclampsia in LMICs, affordability of any novel treatments is a high priority. Current treatments for women with pre-eclampsia (aspirin; calcium supplements) 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 maybe required. Procurement of effective treatments would ideally be

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			prioritized by national governments.
Volume estimates	Volumes compatible with current preventative therapies for pre-eclampsia	Volumes exceeding current preventative therapies for pre-eclampsia	The estimated global incidence of pre-eclampsia is approximately 5%, equating to ~7 million women worldwide each year (though this may be an underestimate). (17) Observational data from the UK report 16.1% of pregnant women are at increased risk of pre-eclampsia. (23) There are currently no reliable global estimates on the coverage of current preventative therapies for pre-eclampsia, though they are widely used.

3 References

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