UPDATED NOVEMBER 2022

Uses of Medicines for Prevention and Treatment of Post-partum Hemorrhage and Other Obstetric Purposes

A Summary of Information on Recommended Uses, Contraindications, and Supply Chain Considerations for Program Managers and Procurement Managers

USAID FROM THE AMERICAN PEOPLE

Reproductive Health SUPPLIES COALITION

ACKNOWLEDGEMENTS

This document was developed by the United States Agency for International Development (USAID) with support from the Global Health Supply Chain - Procurement and Supply Management project and Boston Consulting Group (BCG), in collaboration with the Reproductive Health Supplies Coalition's Maternal Health Supplies Caucus. Special thanks to the following stakeholders for their thought leadership and input:

Beth Yeager, Promoting the Quality of Medicines Plus*

Bonnie Keith, PATH

Debbie Armbruster, USAID

Fiona Theunissen, Concept Foundation

Frank DelPizzo, Boston Consulting Group

Hans Vemer, Concept Foundation

Ian Roberts, London School of Hygiene & Tropical Medicine

Ingrid van Elderen, Ferring Pharmaceuticals

Jane Briggs, Medicines, Technologies, and Pharmaceutical Services Program*

Jeffrey Jacobs, Merck for Mothers, an initiative of Merck & Co., Inc. (U.S.A)

Jill Durocher, Gynuity Health Projects

Kabir Ahmed, UNFPA

Kathleen Hill, Maternal and Child Survival Program*

Laura Frye, Gynuity Health Projects

Mariana Widmer, WHO

Meena Gandhi, DFID

Nic Sukitsch, Boston Consulting Group

Sharif Hossain, Population Council

Siobhan Vega, USAID Global Health Supply Chain Program*

* Funded by USAID

INTRODUCTION

With recent innovations and WHO recommendations, there are now more medication options to prevent and treat post-partum hemorrhage (PPH). However, there is still no single solution for preventing and managing PPH. Countries must determine the appropriate combination of uterotonics, tranexamic acid (TXA), and other life-saving PPH prevention and treatment interventions for use at community, primary, and referral levels. Additionally, these medicines have other important obstetric uses which must be considered.

This brief highlights key characteristics and supply chain considerations for individual uterotonic medicines and TXA that will be used to help program and procurement managers determine the most appropriate combination of medicines for prevention and treatment of PPH and other obstetric indications at different levels of the health system.

BACKGROUND

Post-partum hemorrhage (PPH)—or excessive bleeding after childbirth—continues to be one of the major causes of maternal mortality in low- and middle-income countries, accounting for over a quarter of maternal deaths worldwide. Additionally, PPH morbidity has an impact on women's physical, emotional and economic wellbeing, their reproductive health and choices, and their position in the family and community (e.g. after hysterectomy due to uterine atony). WHO recommends the administration of a prophylactic uterotonic immediately after birth for every woman to help prevent PPH caused by uterine atony (non-contracted uterus). WHO also recommends treatment of PPH with a therapeutic uterotonic and intravenous tranexamic acid (TXA), supplemented by additional interventions based on the cause of the bleeding and the woman’s clinical status (e.g., removal of retained placenta, repair of laceration, blood transfusion, aortic compression, and surgical intervention if bleeding is not controlled.)

Some medicines for prevention and treatment of PPH have been well-known for decades (i.e., oxytocin, ergometrine, and misoprostol) while others are more recent additions. In 2018, WHO updated its PPH treatment recommendations to include the administration of tranexamic acid (TXA) via intravenous route within 3 hours of birth in women with PPH (regardless of the underlying cause of PPH). Also, in 2018, WHO updated its PPH prevention guidelines to include the use of heat-stable carbetocin (HSC) and to provide expanded guidance on the selection of uterotonics for PPH prevention. Some of the uterotonic medicines (oxytocin and misoprostol) have other obstetric uses such as induction and augmentation of labor, while others are actually contraindicated for these uses and may cause harm if used inappropriately.

With an expanding range of uterotonic medicines and TXA to prevent and treat PPH and for other obstetric uses, program managers need clear information in one place on the indications, contraindications, safety profile, and health system requirements for individual medicines to help them make strategic decisions about which medicine to deploy at different levels of the health system based on their country context.

RECOMMENDED AUDIENCE

This information summary is intended for use by those making procurement decisions, including program managers, supply chain managers, and procurement managers for consultation as they consider future procurement and supply chain needs.

Within this audience, sample roles include, but are not limited to, Family Health Division Chief, Maternal and Child Health Program Manager, Supply Chain Manager, Logistics Management Division Chief, Central Medical Store Manager, Hospital Purchasing Manager, and Procurement Officer in the Ministry of Health.

PURPOSE

This brief is intended to serve as a summary of information on the suite of uterotonics and TXA that can be used for the prevention and treatment of post-partum hemorrhage and other obstetric uses. This brief provides background information for the needs of program managers, especially supply chain managers, by summarizing the recommended uses for the medicines currently available and proven effective for prevention or treatment of PPH, other obstetric uses, and the special characteristics of each. These recommended uses and characteristics are elements that may influence procurement and supply chain management decisions. This brief is part of a larger document to guide decision-making around procurement of the appropriate medicines.

It is important to note that this brief is not a replacement for clinical guidelines or global recommendations. Furthermore, this brief should not be interpreted as a job aid for healthcare personnel for the provision of care.

KEY TERMS

Antifibrinolytic agent: A type of drug that helps the blood clot. It prevents the breakdown of a protein called fibrin, which is the main protein in a blood clot. Antifibrinolytic agents may be used to help prevent or treat serious bleeding in patients

Appropriately skilled health personnel: Refers to having health personnel (health providers) present that are skilled to administer IM and/or IV injections, as dictated by each medicine's recommended administration

Coagulant: Agent used to induce contraction or greater tonicity of the uterus

Cold chain: System of storing and transporting medicines at recommended temperatures (temperatures between 2 & 8 degrees Celsius) from point of manufacture to the point of use

Contraindications: Specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the patient

Ergometrine: Refers to both ergometrine or methylergometrine, per WHO recommendations

Induction of Labor: The process of artificially stimulating the full term uterus to start labor . It is usually performed by administering oxytocin or prostaglandins to the pregnant woman or by manually rupturing the amniotic membranes. A health care provider might recommend labor induction for various reasons, primarily when there's concern for a mother's health or a baby's health

IV Infusion set: Consists of a pre-filled, sterile container (plastic bag) of fluids with an attachment that allows the fluid to flow one drop at a time; a long sterile tube with a clamp to regulate or stop the flow; and a connector to attach to the access device

Not recommended: This category indicates that the intervention or option should not be implemented

Prostaglandin: Any of a group of hormone-like fatty acids found throughout the body that affect blood pressure, metabolism, body temperature, and other important body processes

Post-partum Hemorrhage: Blood loss of 500 ml or greater after vaginal delivery and 1000 ml or greater after cesarean section

Uterotonic: Agent used to induce contraction or greater tonicity of the uterus

WHO prequalified product*: List of approved products, determined by WHO Prequalification Team: medicines, who ensures that active pharmaceutical ingredients and finished pharmaceutical products are safe, appropriate and meet stringent quality standards. It does so by assessing product dossiers or master files, inspecting manufacturing and clinical sites, and organizing quality control testing of products

*Note that there are many stringent regulatory authority (SRA) approved medicines available in LMIC markets, but this brief does not identify each medicine

SUMMARY OF RECOMMENDED USES AND HEATH SYSTEM CONSIDERATIONS

This following table summarizes the uses and health system requirements of individual uterotonic medicines and TXA. A selection of these medicines are proven to be effective for the prevention or treatment of PPH and other common obstetric indications. For greater detail on each medicine, including contraindications, characteristics, and safety considerations, please see pages 5-9

Recommended Uses & Health System Factors	Medicines proven effective for prevention or treatment of PPH and other obstetric purposes				
	Oxytocin	Misoprostol	Heat-stable Carbetocin	Ergometrine[1]	Tranexamic Acid[2]
Prevention of PPH	✓	✓	✓	✓	✗
Treatment of PPH	✓	✓	✗	✓	✓
Induction of labor	✓	✓	✗ *Contraindicated*	✗ *Contraindicated*	✗
Augmentation of labor	✓	✗ *Contraindicated*	✗ *Contraindicated*	✗ *Contraindicated*	✗
Post-abortion and miscarriage care	✗	✓	✗	✗	✗
Administration route	IV, IM	Oral, Sublingual	IV, IM	IV, IM	IV
Cold chain requirement	**Yes**	**No**	**No**	**Yes**	**No**
Skilled healthcare personnel required	**Yes**	**No**	**Yes**	**Yes**	**Yes**

✓ Recommended ✗ Not recommended ✗ Contraindicated

IV=Intravenous IM=Intramuscular

1. Note: Use of ergometrine is contraindicated in women with hypertensive disorders. "Ergometrine" refers to ergometrine/methylergometrine. 2. Careful labeling and storage is required to ensure TXA is not mistaken for regional anesthesia (bupivacaine). See FDA and WHO safety alerts

OXYTOCIN

RECOMMENDED USES AND DOSAGE

Prevention of PPH	✓	In settings where multiple uterotonics are available and the quality of oxytocin can be guaranteed, the use of oxytocin is recommended for prevention of PPH → Recommended quantity per patient: 1 ampoule of 10 IU
Treatment of PPH	✓	Intravenous oxytocin is the recommended uterotonic drug for the treatment of PPH → Recommended quantity per patient: 2 ampoules of 10 IU
Induction of labor	✓	If prostaglandins (e.g., misoprostol) are not available, intravenous oxytocin alone should be used for induction of labor → Recommended quantity per patient: 1 ampoule of 10 IU
Augmentation of labor	✓	Use of IV oxytocin alone for treatment of delay in labor is recommended → Recommended quantity per patient: 1 ampoule of 10 IU Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Post-abortion and miscarriage care	✗	Not recommended

PRODUCT CHARACTERISTICS

Presentation	• 10 IU ampoule
Administration	• Intramuscularly or intravenously • For induction and augmentation of labor: IV infusion only
Storage and Transport	• Must be stored at 2 to 8 degrees Celsius
Price per unit	• UNFPA catalogue: USD 0.334 per ampoule
Supplies required	• Syringes, needles, and IV infusion set (for IV only)
Availability	• Currently 4 WHO prequalified products available

HEALTH SYSTEM IMPLICATIONS

Type of Health Facility	• Should only be administered at health facilities where appropriately skilled health personnel are present
Supply Chain	• Should be procured in 10 IU ampoules, not 5 IU ampoules (minimize complexity and maximize efficiency, as unit costs are the same) • Requires functional cold chain and transport—from manufacturer to the point of entry and during distribution to, and storage at, health facilities • Care should be taken to procure quality-assured oxytocin (labelled for storage at 2 to 8 degrees Celsius), as there is high prevalence of poor quality in the public and private sector
Administration & Safety Concerns	• When oxytocin is used for PPH prevention, using oxytocin for PPH treatment may require an additional medicine to be administered to address bleeding

MISOPROSTOL

RECOMMENDED USES AND DOSAGE

Prevention of PPH	✓	In settings where skilled health personnel are not present to administer injectable uterotonics and oxytocin is unavailable or its quality cannot be guaranteed, misoprostol is recommended → Recommended quantity per patient: 400 mcg or 600 mcg oral
Treatment of PPH	✓	Recommended when oxytocin is not available, its quality cannot be guaranteed, or if bleeding does respond to oxytocin → Recommended quantity per patient: 800 mcg oral
Induction of labor	✓	Oral or vaginal misoprostol is recommended for induction of labor → Recommended quantity per patient: 25 mcg oral or vaginal Inappropriate use can contribute to serious morbidities
Augmentation of labor	✗	Contraindicated - Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Post-abortion and miscarriage care	✓	Recommended for post-abortion and miscarriage care → Recommended quantity per patient: 400 mcg sub-lingual or 600 mcg oral

PRODUCT CHARACTERISTICS

Presentation	• 200 mcg oral tablets • 25 mcg oral or vaginal tablets
Administration	• Orally for PPH prevention; sublingually for PPH treatment • Orally / sublingually / vaginally for post-abortion and miscarriage care • Orally or vaginally for induction of labor
Storage and Transport	• Can be stored at room temperature at or below 25 degrees Celsius • Must be packaged in double aluminum blisters until used
Price per unit	• UNFPA catalogue: USD 0.25 – 0.32 per oral tablet of 200 mcg; no price listed in catalogue for 25 mcg presentation
Supplies required	• None
Availability	• Currently 4 WHO prequalified products available

HEALTH SYSTEM IMPLICATIONS

Type of Health Facility	• Can be administered without the presence of skilled health personnel
Supply Chain	• Care should be taken to procure and keep misoprostol packaged in double aluminum blisters until use to reduce the risk of exposure to moisture. • Care should be taken to procure quality-assured misoprostol, as there is high prevalence of poor quality in the public and private sector
Administration & Safety Concerns	• The lack of availability of the 25 mcg presentation may cause providers to attempt to cut a 200 mcg tablet into the appropriate dose. This practice should be avoided as achieving a 25 mcg “piece” of a 200 mcg tablet is virtually impossible when done by hand

HEAT-STABLE CARBETOCIN

RECOMMENDED USES AND DOSAGE

Prevention of PPH		Recommended when cost is comparable to other effective uterotonics in settings where oxytocin is unavailable or its quality cannot be guaranteed → Recommended quantity per patient: 100 mcg
Treatment of PPH		Not recommended
Induction of labor		Contraindicated - Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Augmentation of labor		Contraindicated - Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Post-abortion and miscarriage care		Not recommended

PRODUCT CHARACTERISTICS

Presentation	• 100 mcg in 1 ml ampoule
Administration	• Intramuscularly or slow intravenously (over one minute)
Storage and Transport	• Can be stored at temperatures at or below 30 degrees Celsius
Price per unit	• WHO, Merck for Mothers and Ferring Pharmaceuticals have signed an agreement to make the product available at an affordable and sustainable subsidized price of USD 0.496 per ampoule for the public sector of low & lower-middle income countries
Supplies required	• Syringes, needles, IV infusion set (for IV only)
Availability	• Currently 1 WHO prequalified product available

HEALTH SYSTEM IMPLICATIONS

Type of Health Facility	• Should only be administered at health facilities where appropriately skilled health personnel are present
Supply Chain	• Transported and stored at ambient temperature
Administration & Safety Concerns	• Since the use of HSC for prevention of post-partum hemorrhage is a new recommendation, the product will need to go through the process of introduction and scale-up in the health system

ERGOMETRINE[1]

RECOMMENDED USES AND DOSAGE

Prevention of PPH		Recommended in contexts where quality oxytocin cannot be guaranteed and where hypertensive disorders can be safely excluded before use → Recommended quantity per patient: 200 mcg
Treatment of PPH		Recommended when oxytocin is not available or when bleeding does not respond to oxytocin and a hypertensive disorder can be safely excluded prior to use → Recommended quantity per patient: 200 mcg
Induction of labor		Contraindicated - Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Augmentation of labor		Contraindicated - Inappropriate use can contribute to serious morbidities, including uterine rupture, fetal asphyxia or fetal demise
Post-abortion and miscarriage care		Not recommended

PRODUCT CHARACTERISTICS

Presentation	• Ergometrine maleate 200 mcg/ml injection in 1ml ampoule • Methylergometrine maleate 200 mcg/ml injection in 1 ml ampoule
Administration	• Intramuscularly or intravenously
Storage and Transport	• Must be stored at 2 to 8 degrees Celsius and kept away from light
Price per unit	• UNFPA catalogue: USD 0.582 per ampoule
Supplies required	• Syringes, needles, and IV infusion set (for IV only)
Availability	• Currently no WHO prequalified products available

HEALTH SYSTEM IMPLICATIONS

Type of Health Facility	• Should only be administered at health facilities where appropriately skilled health personnel are present and where women's blood pressure can be monitored
Supply Chain	• Requires a functional cold chain—from the manufacturer to the point of entry and during distribution to, and storage at, health facilities. • Critical that the medicine is protected from light—ergometrine is more sensitive to heat and light than oxytocin • Care should be taken to procure quality-assured ergometrine, as there is high prevalence of poor quality in the public and private sector
Administration & Safety Concerns	• Use of ergometrine is contraindicated in women with hypertensive disorders, elevated BP or in settings where BP cannot be monitored accurately • Other options may have a better side effect profile

1. "Ergometrine" refers to ergometrine / methylergometrine

TRANEXAMIC ACID

RECOMMENDED USES AND DOSAGE

Prevention of PPH	✓	Not recommended
Treatment of PPH	✓	Early use of IV TXA (within 3 hours of birth) in addition to standard care with uterotonics is recommended for women with clinically diagnosed PPH following vaginal birth or caesarean section → Recommended quantity per patient: 1g by IV injection Second dose may be needed if bleeding is persistent
Induction of labor	✗	Not recommended
Augmentation of labor	✗	Not recommended
Post-abortion and miscarriage care	✗	Not recommended

PRODUCT CHARACTERISTICS

Presentation	• 1g in 1 ampoule of 10 ml
Administration	• Intravenously, in complement with uterotonics
Storage and Transport	• Heat stable with no special storage requirements
Price per unit	• No price listed in UNFPA catalogue; USD 2.19 per ampoule per USAID wholesale price
Supplies required	• IV infusion set, syringes and needles
Availability	• Currently no WHO prequalified products available

HEALTH SYSTEM IMPLICATIONS

Type of Health Facility	• Should only be available at health facilities where appropriately skilled health personnel are present
Supply Chain	• TXA is available on many countries' essential medicine list (EML), with trauma as the clinical indication; Countries should update EML to specify PPH treatment as one of the indications for administration of IV TXA
Administration & Safety Concerns	• Tranexamic acid complements uterotonics—it is not a substitute • Tranexamic acid is not a uterotonic—it is a coagulant and antifibrinolytic agent • Careful labeling and storage required so not mistaken for anesthesia (bupivacaine)

REFERENCES

Global Causes of Maternal Death: A WHO Systematic Analysis. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels JD, et al. Lancet Global Health. 2014;2(6): e323-e333.

WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.WHO http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1

WHO recommendations for induction of labour. 2011. http://apps.who.int/iris/bitstream/ handle/10665/44531/9789241501156_eng.pdf?sequence=1

WHO recommendations for augmentation of labour. 2014. http://apps.who.int/iris/bitstream/ handle/10665/112825/9789241507363_eng.pdf?sequence=1

International Medical Products Price Guide. Management Sciences for Health. 2016 http://mshpriceguide.org/en/home/

UNFPA Procurement Services Product Catalogue. Accessed 11/11/18https://www.unfpaprocurement.org/catalog?id=OXYTOCIN _10IU/ML

Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle- income countries: a systematic review of the literature. BJOG Int J Obstet Gynaecol. 2016;123(13):2076-2086. doi:10.1111/1471-0528.13998

Hogerzei, H; Godfrey, P. Instability of (methyl)ergometrine in tropical climates: an overview. European Journal of Obstetrics & Gynecology and Reproductive Biology 69 (1996) 25 29.

International Medical Products Price Guide. Management Sciences for Health. 2016 http://mshpriceguide.org/en/home/

WHO Essential Medicines List 2017. http://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1

WHO: Safe abortion: technical and policy guidance for health systems. 2012 https://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/

UNFPA Procurement Services Product Catalogue. Accessed 11/11/18 https://www.unfpaprocurement.org/catalog? id=MISOPROSTOL_200MG

Widmer M, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med 2018; 379:743-752.

Updated WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Haemorrhage. October 2017. http://apps.who.int/iris/bitstreamhttp://apps.who.int/iris/bitstream/handle/10665/259379/WHO-RHR-17.21-eng.pdf?sequence=1/ handle/10665/259379/WHO-RHR-17.21-eng.pdf?sequence=1

WHO Drug Information Vol. 30, No. 1, 2016, Quality of misoprostol. https://www.who.int/medicines/publications/druginformation/WHO_DI_30-1_Quality.pdf

USAID Global Health Supply Chain Program. Guidelines: Buy Quality Oxytocin, Keep it Cold. https://www.ghsupplychain.org/resource/buy-quality-oxytocin-keep-it-cold