Introducing Oxytocin in the Uniject™ Device

An Overview for Decision Makers

September 2008

1455 NW Leary Way
Seattle, WA 98107-5136 USA
Tel: 206.285.3500 Fax: 206.285.6619
www.path.org

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Using this Document

This overview has been developed for program planners considering introduction and/or expansion of the use of oxytocin, and in particular oxytocin packaged in the Uniject™[1] device, to reduce the incidence of postpartum hemorrhage (PPH) as a component of their maternal and child health programming as well as for treatment of PPH.[2] Administering oxytocin is just one component of active management of third stage labor (AMTSL). AMTSL includes three steps:

1. Administration of a uterotonic drug (i.e., oxytocin, 10 IU injection given intramuscularly).
2. Controlled cord contraction.
3. Uterine massage after delivery of placenta.

More information on this topic can be found in the World Health Organization (WHO) resource *WHO Recommendations for the Prevention of Postpartum Haemorrhage* as well as resources on web sites for Prevention of Postpartum Hemorrhage Initiative (POPPHI) and other organizations.[3,4]

The objective of this resource is to help policymakers and program managers determine if introducing oxytocin in the Uniject prefill injection device (hereafter called Uniject) is appropriate for their program. To guide this decision-making process, this document will provide an overview of the issues and include background on oxytocin in the Uniject device, considerations for introduction, information on program planning, and an outline of key messages for training health workers on use of the device.

Background on Oxytocin in the Uniject Device

Using Oxytocin for Management of the Third Stage of Labor

Hemorrhage is the leading cause of maternal mortality and is a particular problem in many home deliveries because the short response time required for care makes referral impossible in many cases. The percentage of maternal deaths due to postpartum hemorrhage has been reported as 25 percent in sub-Saharan Africa, 27 percent in West Africa, and 45 percent in Indonesia. Annually, approximately 130,000 women are known to die due to hemorrhage during childbirth.[5]

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[1] Uniject is a registered trademark of BD.
[2] WHO. http://www.who.int/reproductive-health/impac/Symptoms/Vaginal_bleeding_after_S25_S34.html. Accessed 9/17/08.
[3] WHO. WHO Recommendations for the Prevention of Postpartum Haemorrhage. 2006. http://www.pphprevention.org/files/WHORecommendationsforPPHaemorrhage.pdf.
[4] POPPHI web site. http://www.pphprevention.org/about.php. Accessed 9/1/08.
[5] JHPIEGO. Preventing Postpartum Hemorrhage: Active Management of the Third Stage of Labor - A Maternal And Neonatal Health Program Best Practice. http://www.reproline.jhu.edu/English/6read/6issues/6jtn/v4/tn110hemor.htm. Accessed 9/15/08.

The use of oxytocin for routine management of the third stage of labor can significantly reduce the incidence of PPH. WHO recommends:

- Routinely offering AMTSL, which includes routine use of a 10 IU dose of oxytocin given intramuscularly, to all women giving birth in facilities or at home when attended by a health care provider with midwifery skills.[6]
- Routinely offering oxytocin in the absence of AMTSL to all women giving birth in facilities or at home when attended by a health worker trained in its use.[6]

Uniject Prefill Injection Device

Use of the autodisable (AD), prefill, single-dose injection device, Uniject, is emerging as an important tool for increasing coverage of immunizations and therapeutics and strengthening safe injection practices in underserved populations. It can be used safely and effectively to address some of the factors contributing to PPH.

The Uniject device (example shown: tetanus toxoid vaccine).

Uniject was designed with the following features:

- **Single dose**—to minimize wastage and facilitate outreach to individual patients.
- **Prefilled**—to ensure that the correct dose is given and to simplify procurement and logistics.
- **Nonreusable**—to minimize patient-to-patient transmission of bloodborne pathogens through needle reuse.
- **Easy to use**—to allow use by health workers who do not normally give injections.
- **Compact size**—for easy transport and disposal.

The features and benefits of Oxytocin in Uniject will help programs launch innovative approaches to expand PPH prevention and treatment such as:

[6] WHO. WHO Recommendations for the Prevention of Postpartum Haemorrhage. 2006.

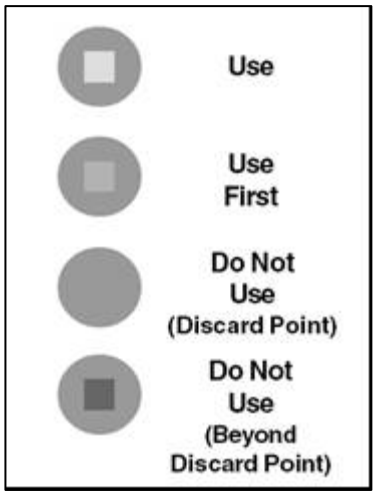
- Administration by skilled midwives, auxiliary nurses, or other trained lay providers.
- Use in areas of limited health facility infrastructure and/or health worker shortages.
- Overcoming acceptability concerns including fear of injections and safety concerns regarding reuse of needles.

Oxytocin in Uniject

As one part of its work to make important vaccines and essential drugs available in Uniject, PATH has been working with stakeholders, donors, and pharmacuetcial collaborators to make oxytocin in Uniject available for public health program introduction. This injection-ready format ensures that an accurate premeasured dose is given in a nonreusable, sterile device with minimal preparation and minimum waste. These benefits may greatly improve the ability of midwives and other trained units to administer oxytocin safely as part of PPH prevention initiatives, including AMTSL initiatives, to women giving birth in facilities—particularly peripheral—and to the large numbers of women giving birth outside clinic or hospital settings. Oxytocin in Uniject may also be ideal for use in emergency situations and remote locations.

Because oxytocin is a heat-sensitive drug, PATH has asked its pharmacuetical collaborators to include a time-temperature indicator (TTI) as part of their oxytocin in Uniject products. Incorproating the TTI will enable a more flexible approach to transport and storage, allowing programs to maximize the field utility of oxytocin in Uniject. Similar to a vaccine vial monitor (VVM) used in immunization programs, the TTI can be added to the packaging of each oxytocin in Uniject dose to allow precise monitoring of cumulative temperature exposure.

Uniject packages with TTIs.



Stages of the TTI.

Some of the benefits of introducing oxytocin in Uniject are detailed below:

Ease of use and wastage reduction

- A prefilled Uniject device replaces a vial, syringe, and needle.

- The prefilled format simplifies ordering, ensures that a sterile syringe and needle are available with each dose of drug, ensures that the loaded syringe is available within one minute after birth of the baby, and minimizes labor costs (e.g., preparation of drugs and syringes for injection).
- The oxytocin in Uniject units are prefilled with oxytocin which means that the provider does not have to:
    - Break open ampoules. Ampoules are sometimes very hard to open and this may result in providers getting cuts from broken glass and/or wastage of ampoules.
    - Open a sterile needle/syringe and measure out the right dose. Some cadres may find it challenging to load syringes.

Expanding program reach

- Oxytocin in Uniject can be used for facility and home births.
- Oxytocin in Uniject can be used by both highly trained and less trained health care providers.
- Oxytocin in Uniject can be used for AMTSL or, where skilled birth attendants are not available, can be offered by a health worker trained in its use for prevention of PPH.[3]
- Oxytocin in Uniject can be used for management and treatment of PPH.[7]
- Oxytocin in Uniject can be used in areas of limited health facility infrastructure and/or health worker shortages.

Improving patient safety

- Use of oxytocin in Uniject reduces the risk of transmission of bloodborne pathogens. Reuse of needles continues to be a serious safety concern in manay countries. As with other AD syringes, the likelihood of patient-to-patient transmission of bloodborne pathogens via syringe and needle reuse or improper sterilization is greatly reduced and results in long-term savings to health programs.
- Lowering the risk of incorrect doses being administered. There is increased assurance that the right dose will be administered with a Uniject device prefilled with a 10 IU dose of oxytocin. In some countries, oxytocin is procured in both 5 IU and 10 IU ampoules. In countries where 5 IU ampoules are used, some providers have been known to give only one (5 IU) instead of two ampoules (the recommended dose of 10 IU) for both AMTSL and treatment of PPH.
- The device can also minimize the risk of abuse of oxytocin. It is nearly impossible to be abused by providers wishing to augment labor by providing 5 IU intramuscularly during labor because of the way the product packaged in the Uniject device. In some countries ministries of health have been reluctant to authorize the use of oxytocin by certain cadres of providers, even for AMTSL. The concern is that providers will use

[7] WHO. Managing complications in pregnancy and childbirth: A guide for midwives and doctors. WHO: Geneva, 2003. (http://www.who.int/reproductive-health/impac/Symptoms/Vaginal_bleeding_after_S25_S34.html. Accessed 8/25/08.

small doses of oxytocin for augmentation if it is available at health centers and providers are authorized to use it. Having oxytocin in Uniject should reduce some of these fears and potentially increase uptake of AMTSL. Uniject can not reasonably be used to administer less than its full 10 IU dose of Oxytocin.

Strengthening the quality of administered oxytocin with use of a TTI

- Use of a TTI enables providers to immediately determine if oxytocin has been exposed to heat levels that will reduce its efficacy.
- TTIs facilitate outreach by making oxytocin in Uniject units available for home births or in facilities that have no cold chain available.

Studies to Date

Four studies have been implemented to date to using the Uniject device to administer oxytocin to women for routine management of the third stage of labor to reduce the incidence of PPH. Studies have shown that oxytocin in Uniject can play a major role in facilitating adoption of AMTSL strategies, thus preventing maternal mortality due to hemorrhage.

Use of the Uniject device in the field for vaccine delivery.

In addition to training and logistical issues, acceptability of this method to women and health care providers has been assessed. Additional studies have assessed the feasibility and acceptability of using oxytocin in Uniject in facility-based and community-based settings by both skilled health workers and specially trained community members.

- Angola—Karolinska Institute, in collaboration with the WHO Safe Motherhood Programme, conducted a study in Angola in which midwives in two maternity units (one central and one peripheral) used 1,500 oxytocin-filled Uniject devices.[8]
- Indonesia—PATH, with funding from USAID and in collaboration with WHO/Indonesia and the Indonesian Ministry of Health, conducted a second study in Indonesia. In this study, village-based midwives successfully used 2,200 oxytocin-filled Uniject devices during home deliveries. Midwives found oxytocin in Uniject to be safer and more convenient to use during home deliveries than traditional needle and syringe.
- Vietnam—PATH and the Ministry of Health of Vietnam, with support from the Bill & Melinda Gates Foundation, assessed the effectiveness of AMTSL to reduce PPH in six districts of Vietnam. This study included a total of 3,607 women (1,236 in the AMTSL intervention district and 2,371 in the comparison district). Oxytocin was administered to women by midwives using either ampoules and syringes or in the Uniject in the AMTSL district. Uterine massage and controlled cord traction were also implemented. The study demonstrated that AMTSL leads to a measurable reduction in the rate of PPH and reduces the need for extra treatment. AMTSL was equally effective with either device, thus confirming that the Uniject device delivers a comparable dose of oxytocin.[9]
- Mali—In three districts in Mali, oxytocin was administered as part of AMTSL to about 15,000 women giving birth in referral and community-level health centers in 2007. Matrones (auxiliary midwives with about six months training) were able to successfully deliver the oxytocin with no more problems than more highly trained midwives, obstetric nurses, and physicians. There were also no additional complications related to misuse of oxytocin in the health centers where oxytocin in Uniject was administered for AMTSL. Having oxytocin in a prefilled format with an assured dose can potentially reduce the risk of misuse, which remains a serious concern for the government as they consider allowing auxiliary midwives to administer the drug for the prevention of PPH.[10]
- In addition, the Uniject device has been used to successfully deliver vaccines such as tetanus toxoid and hepatitis B as well as injectable contraceptives.[11] Key findings from vaccine applications include the ability to expand reach of immunization programs by facilitating outreach and enabling health workers with lower skill levels to administer vaccines.

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[8] Strand RT, et al. Postpartum hemorrhage: a prospective, comparative study in Angola using a new disposable device for oxytocin administration. Acta Obstetricia et Gynecologica Scandinavica. 2005:84:260–265.

[9] Tsu VD, Tran TP, Mai et al. Reducing postpartum hemorrhage in Vietnam: Assessing the effectiveness of active management of the third stage of labor. *J Obstet Gynaecol Res.* 2006:32(5) :489-496.

[10] S. Engelbrecht, PATH/Seattle, personal communication, August 2008

[11] PATH. HealthTech Historical Profile: The Uniject Device. June 2005

Determining if Oxytocin in the Uniject Device is Appropriate for Your Program

In determining if oxytocin in Uniject is appropriate for your program, it is critical to consider the following:

- What are your program's objectives are for introducing oxytocin in Uniject and how it will be used:
    - Introduction of oxytocin as part of AMSTL?
    - Prevention of PPH without AMTSL?
    - Treatment of PPH?

  Programs will be at different stages in the implementation of uterotonics and AMSTL to reduce PPH. Depending on where a program is, different steps will be needed to introduce oxytocin in Uniject.
- Where oxytocin in Uniject will be used:
    - Hospitals?
    - Health centers?
    - Outreach to homes?

  Depending on a program's needs and objectives, introducing oxytocin in Uniject can have different impacts at different levels of a health system and require different steps to ensure that policies are in place to support introduction.
- Who administer oxytocin in Uniject:
    - Skilled birth attendants (doctors, midwives, nurses with midwife skills)?
    - Auxiliary midwives?
    - Health workers trained in the use of uterotonic drugs for the prevention of PPH?
    - Traditional birth attendants?

  If programs are trying to include less-trained health workers to increase access to uterotonic use for prevention of PPH, then oxytocin in Uniject's ease of use and safety features could provide great benefits. Stakeholder support is necessary and a change in policy may be needed.
- What type of cold chain management system is in place to support introduction of oxytocin in Uniject in hospitals and at the community level:
    - Strong system?
    - Limited system?

  Because all oxytocin is heat-sensitive, the addition of a TTI may enable a more flexible approach to transport and storage, allowing programs to maximize the field utility of oxytocin in Uniject.
- What will be the costs of introducing oxytocin in Uniject:
    - How many units will be needed?
    - How many staff will need to be trained?

- What cold chain equipment will be needed to maintain the stability of oxytocin? Should TTIs be included?

Oxytocin in Uniject will cost more than an ampoule of oxytocin and a separate disposable, AD syringe. However a country needs to weigh the benefit of increasing safety and the potential to markedly expand the use and reach of PPH prevention programs through the use of the life-saving drug oxytocin, with or without AMTSL.

Planning for Introduction

It is important to recognize that countries and country programs will be at different stages in the use of uterotonics and AMSTL to reduce PPH. Depending on where a program is, different steps will be needed to introduce oxytocin in Uniject. Below are some examples of approaches that may be needed to move forward with introduction of oxytocin in Uniject.

- **Incorporating oxytocin in Uniject into practice guidelines**—Significant effort may be needed to establish a supportive policy climate if oxytocin is not widely used already or if guidelines are being expanded to support use in outreach by trained birth attendants or other trained injection providers.
- **Piloting use of oxytocin in Uniject—**Before committing to national use in a country, some programs may want to pilot its use to help determine what settings are optimal and what challenges will need to be addressed prior to widespread introduction.
- **Introducing oxytocin in Uniject in health facilities—**Programs may decide that oxytocin in Uniject could have significant impact in health facilities. Safety, ease of use and other factors could contribute to increased used for prevention of PPH as well as treatment. Oxytocin in Uniject could be a catalyst for raising awareness and stimulate increased practice of AMTSL.
- **Introducing oxytocin in Uniject for community-based programs**—Many country public health managers do not feel comfortable scaling up community-based programs requiring injections if these injections will be given by less-skilled health workers using traditional ampoules and syringes. The safety, ease of use, and integrated dose and device features of oxytocin in Uniject may, as has been demonstrated with hepatitis B vaccine in Uniject, provide program managers with the confidence necessary to allow less-trained, more broadly distributed health workers to give an oxytocin injection during the appropriate stage of labor.

More detailed planning tools are becoming available for programs ready to introduce oxytocin in Uniject and will be compiled as part of a larger tool kit. These will include sample protocols for pilot introduction, tools for assessments in advance of introduction, and resources to support procurement planning and logistics—from cold chain management to safe disposal.

Regulatory Framework

Uniject is not registered and approved as a separate, stand-alone device under medical device regulation. Uniject and all other prefilled syringe systems available from pharmaceutical companies are regulated as primary container packaging under pharmaceutical product regulation. Thus there is no general "Uniject registration"—Uniject becomes "approved" only when a pharmaceutical producer applies for regulatory approval for a specific drug using the Uniject device as a primary container.

Current Availability

PATH is actively working with two pharmaceutical companies to make oxytocin in Uniject available. In August 2007, PATH's collaborator, BIOL of Argentina, submitted its dossier for registration of its oxytocin in Uniject with the Argentine Food and Drug Administration and will receive Argentine regulatory approval by fall 2008. A second pharmaceutical producer, Gland Pharma of India, is currently conducting stability studies of its oxytocin in Uniject and hopes to gain Indian regulatory approval and start supplying product for field studies in India in 2009, with international registrations following in 2010.

Forecast Planning and Procurement

Planning for introduction of oxytocin in Uniject will include detailed forecasting for a procurement plan. It will be critical to know how many doses are needed for coverage of the program area. For those programs replacing oxytocin in traditional syringes, these numbers may be more accessible. For programs introducing oxytocin for the first time, either in facilities or expanding use for community-based programs, estimates will need to be made. The process of forecasting will need to be revisited continually as oxytocin in Uniject use expands. Tools to support forecasting will be included in the upcoming toolkit.

Health System Considerations

Cold chain

Although oxytocin can safely be stored outside a refrigerator for up to three months at 30°C, it is important to consider that the recommended storage temperature of oxytocin is from 2°C to 8°C.[12] Oxytocin is not light sensitive, but it is still a good practice to store it in the dark, if possible. If there is no reliable or consistent means of keeping drugs at the required temperature during transit, oxytocin may be exposed for up to two weeks at no more than 40°C while in transit. Several studies performed by WHO have concluded that oxytocin is more thermostable and photostable than other uterotonic medications.

[12] Use of uterotonic drugs for prevention and treatment of postpartum hemorrhage in tropical climates: Guidance for essential drug and safe motherhood programs. Available at: http://www.pphprevention.org/files/Practicalguidance-secure_000.pdf. Accessed: 8/26/08.

The use of a TTI can serve as a tool to monitor heat exposure of oxytocin, and if used correctly can effectively minimize the use of inactive product. Similar to VVM used in immunization programs, the TTI can be added to the packaging of individual oxytocin doses to allow precise monitoring of cumulative temperature exposure. Because oxytocin has cold chain requirements, the TTI enables a more flexible approach to transport and storage of oxytocin, allowing programs to maximize the field utility of oxytocin in Uniject.

Storage capacity
The integrated syringe in the Uniject device requires more storage volume than separate ampoules of oxytocin. For that reason, volume estimates must be made to see if current cold chain storage capacity is adequate to accommodate a move to oxytocin in Uniject. Vaccines in the Uniject device are presently packaged 125 per box and occupy 3 liters or 24 cm3 per dose, and PATH expects oxytocin to have similar storage volume requirements.

Safe disposal
When planning for introduction of oxytocin in Uniject, programs must include safe disposal of the device. The critical components include containment at the point of injection with a sharps container and planning for safe disposal of the container.

Training

Training is a critical component of successful introduction of oxytocin in Uniject. Training requirements will vary based on the implementation plan (i.e., facility- or community-based) and the level of training of birth attendants.

Training strategies
Different approaches will be needed for training depending on the setting into which oxytocin in Uniject is being introduced, into facilities and or for community-based programs. Considerations include the type of health worker and level of previous training of those using the device, the scale of the introduction and the number of health workers needing training, the need for supportive supervision and in-service training as appropriate.

As use of oxytocin in Uniject becomes more prevalent and is integrated into country practice guidelines, programs should take steps to incorporate training on device use into pre-service curriculum for doctors, midwives, and trained birth attendants.

Resources

PATH and its collaborators are actively developing a wide range of materials, protocols, and planning tools to support evaluation and introduction of oxytocin in Uniject for the treatment and prevention of PPH. Please check the following websites for the most currently available resources:

http://www.path.org/projects/preventing_postpartum_hemorrhage.php
http://www.path.org/projects/uniject.php

Acknowledgements

Support for this project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of the HealthTech Cooperative Agreement # GPH-A-00-01-00005-00 and the POPPHI Cooperative Agreement # GHS-I-00-03-00028-00. The contents are the responsibility of PATH and do not necessarily reflect the views of USAID or the US Government.