



Contraceptive Implants

Description

Introduced almost 30 years ago, contraceptive implants are one of the most effective family planning methods available when used in accordance with approved prescribing information. Implants are thin, flexible rods that are inserted just under the skin of a woman's upper arm and provide sustained contraception, ranging from three to five years.

The Population Council developed the first contraceptive implant—Norplant—which was approved in 1983 in Finland, the country of manufacture. Norplant consisted of six rods (2.4 mm x 34 mm), each containing 36 mg of levonorgestrel (a synthetic progestin similar to the natural female hormone progesterone). Production of Norplant was discontinued in 2008 because the new generation of products—the two-rod implants, Jadelle and Sino-implant (II), and 1-rod implants, Implanon and Nexplanon/Implanon NXT—are easier to insert and remove. Jadelle, which was approved by the USFDA in 1996, consists of two rods (2.5 mm x 43 mm), each containing 75 mg of levonorgestrel. In 1996, Sino-implant (II), a similar two-rod implant with the same amount of active ingredient as Jadelle, was introduced in China. This was followed by Implanon, which was first introduced in 1998 and was approved by USFDA in 2006. This single-rod contraceptive implant (2 mm x 40 mm) contains 68 mg etonogestrel (also a progestin).^{1,2,3,4} A new one-rod implant, Nexplanon, has the same design as Implanon but is also radio-opaque, allowing x-ray detection if the rod is difficult to locate due to deep insertion. Nexplanon also has an improved trocar, the surgical instrument used to insert the rod.⁵

Implants provide long-lasting contraception by suppressing ovulation, impeding sperm transit by thickening the cervical mucus, and altering the endometrial structure.⁶ The duration of contraceptive protection varies by brand: Jadelle is registered to provide contraception for five years, Sino-implant (II) for four years, and Implanon and Nexplanon

for three years. Implant insertion and removal procedures are generally short, uncomplicated, and must be conducted by a well-trained health care provider. After removal, there is no delayed return to fertility for implant users compared to women who do not use contraception,⁷ as the synthetic continuous-release hormones in implants have a short half-life. A new implant can be inserted at the time of removal if continued contraception is desired.

Contraceptive implants can be used by almost all women. Implants are best suited for women who desire a user-independent contraceptive method for birth spacing and limiting. Implants should not be inserted in women during the first six weeks after childbirth if they are exclusively or partially breastfeeding; in women with serious liver disease, problems with blood clots, or unusual vaginal bleeding; or in women who have or have had breast cancer. Contraceptive implants do not provide protection from sexually transmitted infections.⁷

Efficacy

Contraceptive implants are one of the most effective contraceptive methods available.

Annual pregnancy rates are less than 1 percent with all implants.^{2,8,9} Continuation rates are often better for longer-acting methods, including implants, than those for shorter-acting methods.¹⁰ No significant differences are found in contraceptive effectiveness or continuation rates among users of the various contraceptive implants.^{2,8,9}

The major side effect associated with the use of contraceptive implants is a change in bleeding patterns (frequency, duration, and amount). Other potential side effects include weight gain, headaches, abdominal pain, acne, dizziness, nausea, breast tenderness, and mood changes. Rarely, infection at the site of the implant can occur.^{7,11} Ovarian cysts may also occur, but usually do not require treatment.³

Registration status/suppliers

| Product | Manufacturer | Presentation | Registration | WHO Prequalification |
|--------------------|--|---|---|----------------------|
| Jadelle | Bayer HealthCare | Disposable, sterile trocar | Registered in more than 47 countries. Review underway in ten additional countries. | Yes |
| Sino-implant (II)* | Shanghai Dahua Pharmaceuticals Co., Ltd. | Disposable, sterile trocar | Registered in 19 countries. Review underway in ten additional countries. | No |
| Implanon | Merck/MSD | Preloaded, disposable, sterile insertion device | Registered in approximately 80 countries. | Yes |
| Nexplanon | Merck/MSD | Preloaded, disposable, sterile insertion device | Registered in 21 countries. Nexplanon/ Implanon NXT will progressively replace Implanon in all countries in the next few years. | No |

*In addition to the manufacturer's name for the product (Sino-implant (II)), the product is marketed under a variety of names by different distributors: as Zarin by Pharm Access Africa, Ltd.; as TRUST by DKT Ethiopia; and as Femplant by Marie Stopes International.

Current program/sector use

Because of implants' effectiveness and convenience, they are popular and in high demand when available in family planning programs.¹² However, the high upfront commodity cost can be a barrier to access, especially in resource-constrained settings. Still, because they are effective for a number of years (i.e., three to five years), are independent of users' compliance, and do not require frequent resupply, implants are more reliable and more cost-effective compared to other shorter-acting contraceptive methods.¹³

Although use of implants—as a percent of the method mix—remains low worldwide, demand often exceeds supply. In some settings, potential implant users go on waiting lists or choose another method. This suggests that the true demand for implants is unknown because there are not enough supplies and services available to meet demand.¹² Significant increases in procurement of contraceptive implants have been reported worldwide over the last several years.¹⁴ Data gathered by the RH Interchange show that in 2005, approximately 132,000 implants were donated in sub-Saharan Africa. By 2011, donations rose to more than 2.5 million.¹⁵

Contraceptive implants are a practical method for use in all settings, as their insertion and removal require only a minor surgical procedure. An essential element of implant provision is ensuring excellent counseling

before insertion so that women know what potential side effects to expect, how to reliably access removal services, and that implants do not protect against HIV or other STIs.¹

It is also critical that policymakers, donors, and service-delivery groups work together to guarantee that women have access to same-day, affordable implant removal services. This includes ensuring adequate training of providers, providing sufficient commodities for removal, and establishing adequate referral systems—especially for women who receive implants through mobile services or community-based programs.¹⁶

Guidance for effective implant introduction and scale-up is available for providers and managers. An online toolkit on contraceptive implants provides up-to-date and accurate information on training, guidance on best practices, and resources and tools to help improve access to and quality of services: www.k4health.org/toolkits/implants.

Manufacturers

Jadelle is manufactured by Bayer HealthCare.

Sino-implant (II) is manufactured by Shanghai Dahua Pharmaceuticals Co., Ltd.

Implanon and Nexplanon are manufactured by Merck/MSD.

Public-sector price agreements

Jadelle: Public-sector price agreements are in place with organizations such as the US Agency for International Development (USAID), the United Nations Population Fund (UNFPA), and nongovernmental organizations (NGOs) offering family planning. In 2012, Bayer Pharma lowered the price of Jadelle to US\$18/unit in developing countries.

Sino-implant (II): Public-sector price agreements are established with distribution partners. Sino-implant (II) is currently available in the public and NGO sectors at approximately US\$8/unit.

Implanon: Public-sector price agreements have been made through contracts with individual Ministries of Health, USAID, UNFPA, and NGOs. The Implanon Access Initiative was launched in June 2011, and aims to enhance access through improved affordability and financing mechanisms in conjunction with the Pledge Guarantee for Health.

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CycleBeads®

Description

CycleBeads® are a color-coded string of beads that help a woman use the Standard Days Method®, a clinically tested natural method of family planning that enables women to manage their own fertility. CycleBeads® are appropriate for women with menstrual cycles 26 to 32 days long. Using CycleBeads®, a woman can track her menstrual cycle, identify the days when unprotected intercourse is likely to result in pregnancy, and monitor her cycle length. She either uses a barrier method or abstains on her potentially fertile days—identified as days 8–19 of the menstrual cycle—to avoid pregnancy.

A woman can use CycleBeads® by placing the rubber ring on the RED bead on the first day of her period. She moves the ring one bead each day. She abstains or uses a condom when the ring is on any WHITE bead if she does not want to become pregnant. She can have unprotected sex when the ring is on any BROWN bead, as she is not likely to get pregnant on those days. She needs to move the ring to the RED bead again when her next period starts, skipping over any remaining beads.

Efficacy

Research has shown that the Standard Days Method® is more than 95 percent effective with correct use (condoms or abstinence during days 8–19 of the menstrual cycle), and more than 88 percent effective in typical use,¹ similar to a number of other user-directed methods.² Similar levels of efficacy have been found when the method is offered in regular service delivery.³ Further, studies of women who purchased CycleBeads® in the context of social marketing—and thus relied on the CycleBeads® instructional insert and point-of-sale materials for method use—showed that their ability to understand and use the method correctly was equal to that of women who received instruction from a trained provider.⁴ The Standard Days Method® provides 1.5 couple-years of protection (CYPs).

Current program/sector use

To date, the Standard Days Method® and CycleBeads® have been used in more than 50 countries and have been successfully integrated into many existing family planning programs and community networks, resulting in more than two million users worldwide.⁵ The Standard Days Method® does not require special equipment, medical procedures, facilities, or costly commodities, and as a knowledge-based method, it is easy to teach and learn. Thus, it can be offered through a wide variety of programs and by a range of providers—including physicians, nurses, auxiliary nurses, community volunteers, public- and private-sector reproductive health programs, faith-based organizations, and social marketing programs through pharmacies and other retailers—without significant additional resources. This method also addresses the needs of diverse populations with varied religious and ethical beliefs, educational backgrounds, and socioeconomic status. It has no side effects and can be used by women who want a pregnancy, as well as by those who do not. Programs in several countries have found that including the Standard Days Method® and CycleBeads® among the options they offer contributes to contraceptive prevalence, enhances the method mix, and brings first-time users to family planning.³ Given the scientific and programmatic evidence, the Standard Days Method® and CycleBeads® are included in numerous documents of the World Health Organization, the US Agency for International Development (USAID), International Planned Parenthood Federation, and Contraceptive Technology.^{6,7,8,9}

The primary impediment to expanded availability and use of this method is ensuring sufficient supply of CycleBeads®. Because the Standard Days Method® is a relatively new method, governments and implementing partners often do not have data about current use on which to forecast future demand and base estimations for CycleBeads® procurement. However, a toolkit is available to aid countries interested in procuring

CycleBeads® by providing a step-by-step process for estimating the initial supply of CycleBeads® needed in their country. It is available electronically from the USAID | DELIVER PROJECT (email: askdeliver@jsi.com); individuals may also contact irhinfo@georgetown.edu. For additional information, see www.cyclebeads.com and www.irh.org. The fact that CycleBeads® require no special storage facilities, have an indefinite shelf life, and are impervious to environmental conditions make them an ideal product for low-resource settings.

Additionally, up-to-date data on CycleBeads® procurement by country and donor can be found on the Reproductive Health Supplies Coalition's online RHInterchange, which supports pipeline monitoring, commodity management, analysis, and planning for program managers, donors, researchers, and advocates.

Manufacturer/supplier

Cycle Technologies is the licensed manufacturer of CycleBeads®. CycleBeads® have been available since 2003 and are now offered through nongovernmental organizations, faith-based organizations, and public social-marketing programs.

Public-sector price agreements

CycleBeads® are now offered as part of the contraceptive method mix available through the Central Contraceptive Procurement (CCP) Project of the Commodities Security and Logistics (CSL) Division at USAID, and can be ordered by USAID programs alongside other contraceptive methods. Missions can provide funding requests for procurement of CycleBeads® to the CCP project either as field support or as a Modified Acquisition and Assistance Request Document. Orders should be forwarded to the CSL country backstop.

Non-USAID-funded groups interested in purchasing CycleBeads® should contact the manufacturer, Cycle Technologies, directly (see www.cyclebeads.com).

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Diaphragm

The diaphragm is a barrier device that covers the cervix and part of the vaginal wall, preventing pregnancy by blocking sperm from entering the uterus. Traditionally, diaphragms were made of latex, but now most are made of silicone. Diaphragms are made in different sizes (generally four to seven sizes depending on the brand), and a woman must be fitted for the correct size by a clinician. Diaphragms are durable and reusable, making them a low-cost contraceptive method.

The diaphragm is held in place by a flexible rim. To use it, a woman inserts the diaphragm with contraceptive gel before intercourse and leaves it in place for six hours afterwards. The diaphragm can be inserted before sex, but should not be kept in place for more than 24 hours without removing it to wash. Research evaluating the safety and acceptability of continuous use of the diaphragm (still removing once a day for cleaning) is ongoing.^{1,2} Clinical guidelines recommend adding additional contraceptive gel before further acts of intercourse. In addition, women who use the diaphragm must be able to wash and store the device.³

Since it is worn internally, diaphragms offer more discreet protection than other barrier methods such as female or male condoms. As a female-initiated method, the diaphragm provides contraceptive protection without requiring male partner involvement. Although some men report not being aware of the diaphragm during sex, women may choose to discuss this method with their partner depending on the communication and expectations in their relationship. Diaphragms are appropriate for women who cannot or choose not to use hormonal or other long-term contraceptive methods, and for women who want protection only around the time they have sex. Diaphragms are also an appropriate back-up method in case a woman has missed taking oral contraceptive pills or her other method is out-of-stock at the family planning clinic. There are no age or parity restrictions on use, and a woman can use a diaphragm throughout her reproductive life (although the size may need to be checked). Return to fertility is immediate after use. Diaphragms are best suited for a woman who finds using a method near or at the time of intercourse acceptable, can learn the insertion technique, and feels she has sufficient privacy for insertion and removal.

Efficacy

Contraceptive effectiveness depends on correct and consistent use. The diaphragm used with spermicide is 84–94 percent effective in preventing pregnancy during the first year of use.⁴ Due to concern about its effect on the vaginal epithelium, use of spermicide containing Nonoxynol-9 (N-9) is not recommended for women at high risk of HIV infection or women who participate in multiple sex acts on a daily basis.⁵ Several prospective studies that looked at the efficacy of diaphragms without spermicide suggest that spermicide improves efficacy, but to a modest degree.^{6,7,8} While these prospective studies provide evidence that a cervical barrier without spermicides has contraceptive efficacy not dramatically different than that of cervical barriers plus spermicides, definitive information on contraceptive efficacy without spermicides is not available.

Current program/sector use

Challenges

There are a number of obstacles to expanded use of traditional-sized diaphragms. One is the requirement for a clinician fitting; another is the complexity of supplying product in multiple sizes. A reanalysis of fitting data from previous barrier-method clinical trials suggests that many women could be correctly fitted with a one-size diaphragm.⁹ There are currently two single-sized products under evaluation; at least one is expected to be available in some markets in 2012.

Effective use also is dependent upon a continued supply of contraceptive gel. Given concern about increased risk of HIV, many family planning programs in regions with HIV prevalence have stopped supplying products containing N-9. Efforts are under way to identify contraceptive gel alternatives that do not use N-9. Even when an alternative gel is identified and validated, supply and cost issues will remain, which is why reproductive health researchers are interested in evaluating the efficacy and acceptability of the diaphragm without contraceptive gel.

Opportunities

When women receive information from providers and support from their partners, they find diaphragms very acceptable and successful as a method of family planning. Over the past decade, clinical studies in 13 countries have found diaphragms can be used successfully by women in low-resource settings. One report from India emphasized that women can use diaphragms successfully even when they do not have access to private bathrooms or running water in the house.¹⁰ Other studies in Zimbabwe, Kenya, and Madagascar¹¹—as well as Thailand, South Africa, Dominican Republic, and the United States—have found that diaphragms are well-accepted even among women who have no previous experience with the method.^{12,13,14}

A June 2008 online discussion about diaphragm programs worldwide can be accessed by joining the “Cervical Barrier Methods” community at the Knowledge Gateway for Reproductive Health at <http://my.ibpinitiative.org/>. The Cervical Barrier Advancement Society (CBAS) serves as a portal for diaphragm research and information (www.cbas.org).

Manufacturers/suppliers

ORTHO ALL-FLEX® Diaphragm

The ALL-FLEX® is a diaphragm with a shallow dome and a flexible rim with an arcing spring. The ALL-FLEX® Diaphragm is now made from silicone and is available in four sizes (65 mm to 80 mm).¹⁵ It is manufactured by Ortho-McNeil-Janssen Pharmaceuticals, Inc., the world market leader in diaphragm sales and distribution. ALL-FLEX® is available globally, though as of 2008 it has been discontinued in Canada.

Milex™ Wide-Seal Diaphragm

Milex Wide-Seal® Arcing and Omniflex diaphragms are manufactured by Cooper Surgical and are distributed in the United States, Canada, Europe, Asia, and the Middle East. Both styles are available in eight sizes (60 mm to 95 mm) and are made of silicone.¹⁶

Semina Diaphragm

The Semina Diaphragm is a clear, silicone diaphragm with a visible coil spring. It comes in six sizes (60 mm to 85 mm) and is manufactured by Semina Industries and Commerce Ltd. The product is marketed in Brazil.¹⁷

Reflexions Flat Spring® Diaphragm

The Reflexions Flat Spring® is a rubber diaphragm with a rim that is similar to the coil spring but thinner and more delicate. It is available in nine sizes (from 55 mm to 95 mm). Reflexions is manufactured and marketed in Britain.

Public-sector price agreements

None.

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Emergency contraceptive pills

Emergency oral contraceptive pills are a post-coital contraceptive option, allowing women to prevent pregnancy after intercourse has occurred. Low contraceptive-prevalence rates along with high levels of unmet need for family planning in many developing countries indicate a high frequency of unprotected sexual relationships. As a result, many couples are at risk for an unplanned and/or unwanted pregnancy. Emergency contraception (EC) is effective in preventing a substantial proportion of pregnancies when it is used promptly after unprotected intercourse. It is an especially important option in cases of sexual coercion or rape.

The most commonly available regimen is 1.5 mg levonorgestrel in a single dose, packaged either as a single pill or as two pills of 0.75 mg each. Although the two-pill products usually include instructions to take one pill up to 72 hours after unprotected intercourse and the second one 12 hours later, they can both be taken together without increasing side effects; this minimizes the chance of the second dose being missed.¹ This product is on WHO's Model List of Essential Medicines² and is included in many countries' national medicines lists or formularies.

More recently, a regimen containing 30 mg of the compound ulipristal acetate has been made available and can also be taken up to 120 hours after unprotected intercourse.³ As of January 2012, this regimen is not available in developing countries.

Emergency contraceptive pills (ECPs) work mainly by either preventing or delaying ovulation; this is likely the only mechanism of action, although there is some evidence showing that they may prevent the sperm and egg from meeting by altering the cervical mucus.⁴ ECPs are more effective the sooner they are taken. Regular oral contraceptives taken in specific doses also can serve as EC. For a list of regular oral contraceptives that can be used for EC purposes, visit: <http://ec.princeton.edu/worldwide/default.asp#country>.

Efficacy

Depending on the formulation used and timing of use, ECPs can reduce a woman's risk of becoming pregnant from a single act of intercourse between 75 and 89 percent.

Current program/sector use

ECPs are registered and available commercially in a number of countries. They are regulated as an over-the-counter or non-prescription product in many developed and developing countries. Still, many women are not aware of EC, and the pills often are not included in public-sector programs.

ECPs can be provided by pharmacists or pharmacy personnel with minimal or no training. Women can self-diagnose the need for use and can administer the pills without supervision. ECPs can safely be provided over the counter and in a number of countries are regulated for over-the-counter dispensing. They do not require high training or start-up investments when being added to family planning or social marketing programs. However, programs may wish to work to raise women's awareness of this contraceptive option.

Manufacturers/suppliers

There are many manufacturers of ECPs. The International Consortium for Emergency Contraception lists manufacturers in its products database: <http://www.cecinfo.org/database/pill/pillData.php>.

Some (but not all) of these products are of assured quality, either because they have been approved by a stringent regulatory authority* such as the US Food and Drug Administration or the European Medicines Agency, prequalified by WHO, or undergone rigorous quality evaluations as part of a procurement process.

* See www.theglobalfund.org/documents/psm/PSM_CountriesSRA_List_en/ for more information on stringent regulatory authorities.

Registration status

Dedicated ECP formulations are registered in more than 140 countries. For a list of country registrations, please go to the International Consortium for Emergency Contraception site at www.cecinfo.org/database/index.htm.

Public-sector price agreements

Gedeon Richter, the manufacturer of Postinor-2, makes the product available to the public sector (government agencies) at a preferential price. Other manufacturers and distributors have demonstrated a willingness to provide a discounted price to public-sector agencies or NGOs wishing to purchase their products.

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Female condom

Description

The female condom is a condom made of a soft, thin material that fits inside a woman's vagina. Like the male condom, the female condom is a barrier method, keeping the penis and sperm from contact with the cervix and vagina. But unlike the male condom, it also covers parts of the external female genitalia. The female condom offers protection against both unintended pregnancy and sexually transmitted infections (STIs), including HIV.

Current models on the market have a flexible ring, sponge, or capsule containing foam shapes at the closed end of the condom, enabling insertion of the device and helping to keep the condom in place during sex. A ring or frame at the open end of the condom stays outside the vagina, lying flat across the genital area and ensuring that the condom stays in place, as well as protecting from external STIs. The female condom can be inserted into the vagina prior to sexual intercourse, is not dependent on a male erection, and can remain in place after ejaculation. It has no known side effects or risks and can be used by women of all ages.*

The first-generation female condom (FC1®), manufactured by the Female Health Company (FHC), was made from polyurethane—a thin, odorless material that is hypoallergenic, stronger than natural rubber latex, and conducts heat. The FC1® was launched on the market in 1992, but is no longer manufactured and has been replaced by a second-generation product, the FC2®. The FC2® is made of nitrile rubber—a synthetic type of latex—and can be used with any type of lubricant, including oil-, silicone-, or water-based products.

In addition to the FC2®, there are four other female condom models on the market: the VA w.o.w.®, Cupid™, Phoenurse®, and the Woman's Condom. The VA w.o.w.® and the Cupid™ female condoms are both made of natural rubber latex and come pre-lubricated

with silicone, but can also be used with water-based lubricants. Oil-based lubricants cannot be used with natural rubber latex condoms. The Phoenurse® female condom is made of polyurethane; comes pre-lubricated with a silicone-based lubricant; and is packaged with an insertion tool, sanitary towel, and disposable bag. The Woman's Condom is made of thin polyurethane film and is packaged un-lubricated. Each Woman's Condom is supplied with a separate sachet of water-based lubricant to be applied at point of use.†

Efficacy

Data from the 2007 World Health Organization family planning handbook indicates that about 21 pregnancies occur per 100 women using female condoms over the first year. When female condoms are used correctly with every act of sex, about five pregnancies occur per 100 women over the first year.¹ The effectiveness studies these data are based upon were undertaken with the FC1® female condom (no longer on the market), and while one cannot extrapolate this data to all female condoms, they do provide basis for discussion. The World Health Organization and the US Food and Drug Administration have determined that the FC2® is equivalent to the FC1®. Estimates on the contraceptive efficacy of the FC1® are within the range of other barrier protective methods (e.g., male condoms). FC1® maintains lower failure rates than either the cervical cap or diaphragm.

In vitro studies of the FC1® confirm that the product provides an effective barrier against many common STIs, including HIV. Calculations based on correct and consistent use estimate a 97.1 percent reduction in the risk of HIV infection for each act of intercourse.²

Research conducted on the FC1® in Brazil, India, Thailand, the United States, and Zambia indicates an increase of protected sexual acts and decrease in STI

* Women who are allergic to latex are recommended to not use latex female condoms.

† See table below for additional information on currently available brands of female condoms.

Included below are the five female condom products that are on the market:

| Product | Regulatory status/availability | General price estimates ^a | Distribution |
|--|---|---|---|
| <p>FC2® female condom (also known under brand names such as Femidon, Protectiv, Care, and many others).</p> <p>Nitrile (synthetic latex), pre-lubricated.</p> <p>Manufactured by the Female Health Company.</p> | <p>CE marking.</p> <p>WHO prequalified, 2007.</p> <p>USFDA approved, 2009.</p> | <p>US \$0.57/unit; volume discounts may apply.</p> <p>Retail: US\$ 2.00.</p> | <p>Registered and/or distributed in 120 countries.</p> |
| <p>VA w.o.w.® female condom (also known as: Reddy, V'Amour, L'amour).</p> <p>Polyurethane sponge and natural rubber latex, pre-lubricated.</p> <p>Manufactured by Medtech Products Ltd.</p> | <p>CE marking.</p> <p>India Drug Control Authority approval.</p> <p>Registered with Brazilian regulatory agency (ANVISA).</p> <p>USFDA Phase 1 clinical trials completed.</p> <p>Under WHO review for prequalification.</p> | <p>US \$0.23/unit at 35 million units.</p> <p>Retail: US\$1.00</p> | <p>Argentina, Brazil, Germany, India, Indonesia, Portugal, South Africa, Swaziland, and the United Kingdom.</p> |
| <p>Cupid™ Condom</p> <p>Natural rubber latex, pre-lubricated.</p> <p>Manufactured by Cupid.</p> | <p>CE marking.</p> <p>Registered within Brazilian regulatory agency (ANVISA).</p> <p>Under WHO review for prequalification.</p> | <p>US\$0.35/unit at 1 million units.</p> <p>Retail: US \$0.65.</p> | <p>India, plus small-scale distribution in Brazil, Indonesia, the Netherlands, South Africa, and Mozambique.</p> <p>Will be distributed at a large scale in Mozambique from 2012 onwards.</p> |
| <p>Phoenurse® female condom</p> <p>Polyurethane, pre-lubricated.</p> <p>Manufactured by Tianjin Condbao Medical Polyurethane Tech. Co. Ltd, Tianjin, China.</p> | <p>Tianjin Food and Drug Administration approval.</p> <p>Registered within Brazilian regulatory agency (ANVISA).</p> <p>Under WHO review for prequalification.</p> | <p>US\$0.59/unit at 1 million units.</p> <p>Retail: approximately US\$1.80-2.80.</p> | <p>Limited distribution in China.</p> <p>Currently seeking opportunities in South Africa and Brazil.</p> |
| <p>Woman's Condom (also known as O'lavie™ for the China market). Pouch, ring, and foam shapes made of polyurethane; dissolving insertion capsule made of polyvinyl alcohol.</p> <p>Condom is un-lubricated and packaged with water-based lubricant.</p> <p>Manufactured by Shanghai Dahua Medical Apparatus Company, China.</p> | <p>CE marking.</p> <p>Shanghai Food and Drug Administration approval.</p> <p>Under WHO review for prequalification.</p> <p>Undergoing contraceptive effectiveness study needed for USFDA approval.</p> | <p>US\$0.87/unit, volume discounts may apply.</p> <p>Retail in China: approximately US\$2.35.</p> | <p>Limited private-sector distribution in China.</p> |

^a Pricing information in this table is based on the most accurate information and/or estimates available. Prices may fluctuate depending on various procurement conditions, including volume and contractual stipulations.

prevalence when FC1® is available alongside male condoms.^{3,4,5,6,7} In a pilot study from Thailand, protected sexual acts increased from 57 to 88 percent, and STI prevalence decreased from 52 to 40 percent when both male and female condoms were available.⁸

Female condoms are the only female-initiated methods of HIV prevention that are safe and effective. Studies from 40 countries show acceptability rates ranging from 37 to 93 percent.⁹

Current program/sector use

Since 1993, approximately 300 million female condoms have been distributed in 120 countries, and public-sector programs are underway in more than 90 countries. Availability of female condoms, particularly in developing countries, has increased from 14 million units in 2005 to 50 million in 2010.¹⁰ However, based on data in the Reproductive Health Interchange, female

condoms only account for approximately 0.19 percent of global condom procurement.¹¹

The FC2[®] is purchased for public-sector programs by organizations such as the US Agency for International Development, the United Nations Population Fund (UNFPA), and governmental health ministries. The Female Health Company funds a global public-sector team consisting of professional program advisors that work with stakeholders on a pro-bono basis to build strong, comprehensive reproductive health, family planning, and HIV prevention programs. In addition, approximately five million VA w.o.w.[®] female condoms were sold commercially between 2003 and 2007.¹² The Cupid condom has limited distribution in India, Brazil, Indonesia, the Netherlands, South Africa and Mozambique.

The Phoenurse[®] and the Woman's Condom are newer products. Phoenurse[®] entered the Chinese market in 2009. Phoenurse[®] has limited distribution in China and manufacturers are currently working on entering the Brazilian and South African markets. The Woman's Condom, branded O'lavie™ for the China market, has been available since September 2011 in limited private-sector distribution channels.

Manufacturer

The Female Health Company manufactures, markets, and sells the FC2[®]. Medtech Products Ltd. of India manufactures, markets, and sells the VA w.o.w.[®] female condom. Cupid Ltd., also of India, manufactures, markets and sells the Cupid™ condom. Tianjin Kondombao Medical Polyurethane Tech. Co. Ltd. of Tianjin, China, manufactures, markets, and sells the Phoenurse[®] female condom, while Dahua Medical Apparatus Company of Shanghai, China, manufactures, markets, and sells the Woman's Condom.

Registration status

The FC2[®] completed the evaluation process of the World Health Organization's (WHO) Technical Review Committee on female condoms in 2006, making it eligible for procurement by United Nations agencies. In March 2009, FC2[®] received approval by the US Food and Drug Administration (USFDA).¹³ The FC2[®] female condom also has CE marking, which certifies that a product has met European Union consumer safety, health, and environmental requirements.[‡]

The VA w.o.w.[®] female condom, Cupid™ condom, and Woman's Condom all carry CE marking. In addition, the VA w.o.w.[®] and the Cupid™ condoms have

‡ The manufacturer of a product affixes the CE marking to it, assuring the product meets European Economic Area regulations. However, the manufacturers do have to take certain obligatory steps before the product can bear the CE marking: they must complete a conformity assessment, set up a technical file, and sign a European Community declaration of conformity. The document has to be made available to authorities on request.

approval from the India Drug Control Authority and the Brazilian regulatory agency (ANVISA), while the Woman's Condom has approval from the Shanghai Food and Drug Administration in China. The Phoenurse[®] female condom does not have CE marking, but it has received approval from the Tianjin Food and Drug Administration in China and from ANVISA.[§] These latter four female condoms, along with six other female condom designs, are currently under review by the WHO/UNFPA Technical Review Committee to determine their suitability for public-sector purchase.

Public-sector price agreements

FC2[®] was designed to replace the FC1[®] female condom and lower the cost of female condoms for UN agencies, bilateral donors, governments, and nongovernmental organizations. Public-sector pricing information on the VA w.o.w.[®] female condom is not currently available, although it has been supplied in small quantities to public-sector programs in Brazil, Finland, Portugal, Swaziland, South Africa, and Indonesia. The Cupid™, Phoenurse[®], and Woman's Condom female condoms have not been sold to public-sector purchasers as of the date of this publication.

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HPV Vaccines

Description

Two vaccines against human papillomavirus (HPV)—a sexually transmitted virus that causes cervical cancer—were approved in 2006 and 2007, respectively, after more than ten years of intensive research and commercial development. Both vaccines—Gardasil®, the quadrivalent vaccine, and Cervarix®, the bivalent vaccine—prevent infection and precancerous cervical lesions caused by HPV types 16 and 18. Gardasil® also prevents infection with types 6 and 11, which cause genital warts and respiratory papillomatosis. HPV types 16 and 18 account for approximately 70 percent of cervical cancer cases worldwide¹ and a similar proportion of anal cancers.² The USFDA recently also approved the quadrivalent vaccine for use in boys and men 9 to 26 years of age for prevention of anal precancerous lesions, cancer, and genital warts. The vaccines also offer some degree of cross-protection against a few non-vaccine cancer-causing types. Both vaccines are given in a series of three intramuscular injections over a six-month period.

More than half of all sexually active people will contract an HPV infection at some point in their lives, although only a relatively small percentage of women will progress to cervical cancer.^{3,4} However, this translates to an estimated 530,000 women worldwide developing cervical cancer every year and 275,000 dying from the disease.⁵ The vast majority of these women—around 85 percent—live in developing countries, where life-saving services to screen for and treat precancerous lesions are not available (e.g., Pap smears or other screening technologies, followed by treatment). By 2030, cervical cancer is expected to kill more than 474,000 women per year, with more than 95 percent of these deaths in low- and middle-income countries.⁵

Efficacy, target groups for vaccination, and duration of protection

In large, international clinical trials in young adult females, both vaccines were shown to be at least 92 percent efficacious in preventing HPV infections and precancerous lesions caused by vaccine types when administered prior to HPV infection.^{6,7} While efficacy against infection and lesions was not demonstrated in young adolescents (because most were not yet exposed to infection), bridging studies have shown that antibody levels after vaccination are as high or higher in young adolescent females and males⁸⁻¹⁰ as in young adult females. According to the World Health Organization, young adolescent girls aged 10 to 13 years are the primary target group for HPV vaccination because the vaccines are most efficacious in people not yet exposed to the viruses.¹¹ Some countries have also targeted a secondary group for “catch-up” vaccinations, often women aged 14 to 18 years. There is evidence that duration of protection is at least five years for the quadrivalent¹² and more than eight years for the bivalent vaccine¹³ (the length of follow-up studies published to date), and longer-term efficacy is still being evaluated.¹⁴⁻¹⁶

Global use

HPV vaccines are available through the private sector in more than 100 countries and have been introduced into public immunization programs in more than 30 countries. While they are not yet widely available in the developing world, several middle-income countries—including Mexico, Panama, Peru, and Malaysia—and some low-income countries—including Bhutan and

Rwanda—have started national vaccination programs. For information on research into the feasibility, acceptability, and cost of HPV vaccination programs in low-resource settings, visit www.path.org/projects/cervical_cancer_vaccine.php. For publications with practical information on planning for and implementing HPV vaccination programs, see <http://www.rho.org/HPV-vaccine-implementation.htm>.

Manufacturers

Gardasil® is manufactured by Merck & Co., Inc. (www.merck.com). Cervarix® is manufactured by GlaxoSmithKline (www.gsk.com).

In 2009, the World Health Organization “prequalified” both HPV vaccines for procurement by United Nations agencies such as the United Nations Children’s Fund (UNICEF) and the Pan American Health Organization (PAHO) Revolving Fund for Vaccine Procurement.

Registration status

As of April 2011, Gardasil® was approved in 123 countries and Cervarix® in 114. However, licensed vaccines may not yet be marketed in a given country.

Public-sector price agreements

The GAVI Alliance, an immunization coalition of the world’s top global health agencies, governments, and private partners, offers subsidized vaccines to more than 70 countries in the developing world. In 2012, GAVI began offering HPV vaccines as well. GAVI is continuing price negotiations with the two manufacturers, and the lowest publically documented price per dose is US\$5 for the quadrivalent HPV vaccine. Merck & Co., Inc. quoted this price to GAVI in June 2011. Countries requesting GAVI-supported vaccine will be responsible for a co-pay of about US\$0.20 to 0.40 per dose for the vaccine itself, and will be responsible for delivery costs. Now that GAVI has begun subsidizing the vaccine, it is likely—based on recent experience with demonstration projects in Africa, Asia, and Latin America—that many low-resource countries will add HPV vaccine to their national programs. GAVI’s support will put HPV vaccine within reach of the world’s poorest nations.

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Levonorgestrel intrauterine system

Description

The levonorgestrel intrauterine system (LNG IUS) is a T-shaped, plastic, contraceptive intrauterine system (IUS) that releases the progestin hormone levonorgestrel into the uterus at a dose of 20 µg per day for up to five years. LNG IUS prevents pregnancy by thickening cervical mucus, inhibiting sperm motility, and suppressing the growth of the uterine wall.^{1,2,3}

The LNG IUS must be inserted and removed by a qualified medical or health care practitioner using aseptic techniques. A gynaecological examination is advised before device insertion (to screen for infections and exclude pregnancy) and again four to twelve weeks after insertion. Thereafter, annual check-ups are recommended to ensure that the device remains in place and to ensure that the user's needs are being met. There are no age or parity restrictions on its use, and women can use an LNG IUS throughout their reproductive life if it is replaced at the recommended intervals. Removal of an LNG IUS can be done at any time by a qualified medical or health care practitioner. Upon removal, fertility will return rapidly. LNG IUS is best suited for women who desire a long-term, reliable contraceptive method for birth spacing or limiting, and also have access to a qualified medical or health care practitioner for counselling, examination, insertion, and check-ups. The LNG IUS does not provide protection from sexually transmitted infections, including HIV.

Efficacy

The LNG IUS is one of the most effective and long-lasting contraceptive methods available. Over the first year of use, the pregnancy rate is 2 per 1,000 women using an LNG IUS—in other words, 0.2 percent. After the first year, there is a lower risk of pregnancy—cumulatively only 5 to 8 pregnancies per 1,000 women over five years of use.^{4,5}

Complications from LNG IUS use are rare, but may include uterine perforations at the time of insertion,

expulsion due to inappropriate device location, and pelvic inflammatory disease.⁶ Side effects associated with use of the LNG IUS include possible change in bleeding patterns (in frequency, duration, and amount), absence of bleeding, and benign ovarian cysts.

In addition to the protection against pregnancy associated with the use of LNG IUS, there are a number of significant health benefits related to the product's additional indication for the treatment of heavy menstrual bleeding.⁷ These include the reduction of iron-deficiency anaemia, reduced volume of menstrual bleeding, and the lessening of menstrual cramps.⁸ The reduction of menstrual bleeding enabled by LNG IUS is attributable to the product's gradual reduction of the thickness and vascularity of the endometrium over the first three to six months of use. As a result, women who had previously experienced heavy menstrual bleeding noticed a significant reduction of blood loss, of between 79 and 98 percent.⁸ Practically speaking, women using LNG IUS gradually experience lighter menstrual bleeding for fewer days. Because of this additional effect of LNG IUS, a provider may recommend it to women with menorrhagia or who seek to lessen heavy periods.⁷ For more information on LNG IUS, its health benefits, and contraceptive dynamics, see the special issue of the journal *Contraception* on IUS/intrauterine devices of contraception.⁹

Current program/sector use

IUSs are now being introduced in both developed and developing countries and are gaining popularity in a number of countries in South Asia, Africa, and Latin America.¹⁰ Mirena®, an IUS produced by Bayer Pharma, is provided commercially through gynaecologists and other qualified providers in the countries where it is registered. During 2010, approximately 3.17 million units were sold globally, with the largest sales reported in the United States and Europe. Since its introduction into the market, more than 18 million women have selected Mirena® as their method of choice.¹¹ The International Contraceptive Access (ICA) Foundation, founded by

the Population Council and Bayer Pharma, provides a bioequivalent LNG IUS that is now available in 13 countries through the public and nonprofit sector via donations. Specifically, the ICA Foundation is currently providing the LNG IUS for projects in Brazil, Curacao, Dominican Republic, Ecuador, El Salvador, Ethiopia, Ghana, Indonesia, Kenya, Nigeria, Paraguay, Saint Lucia, and South Africa.

Despite the increasing popularity of the LNG IUS, there are several obstacles to its expanded use, including the upfront cost of the product in the private sector. In terms of costs over time, the LNG IUS is among the least expensive contraceptive methods because of its long-term effectiveness, yet the initial cost of the product in the private sector is high.¹² Availability of the product is also a current constraint; the LNG IUS is generally not available in developing countries except through the ICA Foundation. The prevailing policies in many countries are also challenging access, as only certified nurses and medical practitioners are permitted to insert IUDs/IUSs. Authorizing trained allied health workers to carry out this procedure has been shown to be effective and cost-saving in a number of settings.¹³ Eliminating unnecessary follow-up visits may be another way to reduce costs and increase patient acceptability of the IUS. Requiring a clinic follow-up soon after insertion to ensure proper placement and absence of infection is important; thereafter, clinic visits are only recommended in response to negative signs and symptoms, or a woman's desire for removal. This guidance has been shown to be sufficient in treating complications and meeting patients' needs.¹⁴

Manufacturer

LNG IUSs are manufactured in Turku, Finland by Bayer Pharma. The LNG IUS available in the private market as Mirena® is also marketed by Bayer Pharma.

Registration status/suppliers

The Mirena® IUS is registered in more than 120 countries worldwide, distributed commercially by Bayer Pharma, and donated to public-sector organizations in the United States by the Arch Foundation.

The LNG IUS provided by the ICA Foundation is registered in three countries (Ghana, Kenya, and Nigeria), but is available through public-sector

donations with approval by national medical authorities such as the Ministry of Health or National Drug Controller. The LNG IUS uses a different inserter than is used for Mirena® and often requires a different registration.

Public-sector price agreements

The ICA Foundation donates LNG IUSs to international development agencies and public-health organizations (both governmental and nongovernmental affiliates) who then offer the LNG IUS at reduced or no cost to poor women and families.¹⁵ As of December 2011, approximately 40,000 LNG IUS units have been donated by the ICA Foundation.¹⁶

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Magnesium sulfate

Description

Magnesium sulfate is an anticonvulsant drug recommended by the World Health Organization as the most effective, safe, and low-cost treatment available for severe pre-eclampsia and eclampsia. Severe pre-eclampsia is a common cause of maternal death, leading to approximately 50,000 maternal deaths per year.¹ Some early symptoms manifest as headaches, epigastric or right hypochondrial pain, vomiting, and visual disturbances.² If left untreated, the condition can lead to seizures and convulsions (known as eclampsia), hypertension, kidney and liver damage, and death. Teenage mothers in developing countries are most affected by eclampsia, which typically manifests during a woman's first pregnancy and is more common in areas of general poverty and poor access to antenatal and intrapartum care. However, the efficacy and low-cost of magnesium sulfate make this condition a highly treatable one.³

Although its exact mechanism of action is unclear, magnesium sulfate is thought to treat eclampsia through affecting a series of cardiovascular and neurological functions and by altering calcium metabolism.⁴ Some studies have suggested that magnesium sulfate could act as a vasodilator, having actions which relieve vasoconstriction, protect the blood-brain barrier, decrease cerebral edema formation, and act as a cerebral anticonvulsant.⁵

In terms of administering the drug, magnesium sulfate is a solution that can be administered intramuscularly or intravenously, at a recommended concentration of 1.8 to 3.0mmol/L. For intramuscular administration, an initial 4g dose is given intravenously, followed immediately by a 10g intramuscular dose, and then 5g intramuscular doses every four hours in alternating buttocks. For intravenous administration, an initial 4g dose is given intravenously, followed by a 1-2g/h maintenance infusion given by a controlled infusion pump.⁶

Efficacy, safety, and benefits

A three-year study called "the Magpie Trials" was launched in 2002 as a collaborative effort including the World Health Organization, the UK Medical Research Council, and other partners to comprehensively study the efficacy of magnesium sulfate to treat eclampsia. The study was conducted in 33 countries and included nearly 10,000 pre-eclamptic pregnant women. The results of the study were that the women who were given magnesium sulfate had a 58 percent lower risk of eclampsia and a 45 percent lower risk of dying from eclampsia than women who were administered a placebo.^{7,8} These results are consistent with other studies of the drug, notably the 1995 Collaborative Eclampsia Trial, in which the relative effectiveness of magnesium sulfate was compared with Diazepam and Phenytoin (two anticonvulsant drugs commonly used to treat eclampsia), validating the significantly higher efficacy rate of magnesium sulfate in the treatment of eclampsia and in the prevention of recurring seizures. Women administered magnesium sulfate had a 52 and 67 percent lower rate of convulsions than those treated with Diazepam and Phenytoin, respectively.^{9,10,11}

When magnesium sulfate is carefully administered and closely monitored, the toxicity of this treatment is minimal (<2 percent). Magnesium sulfate is nearly entirely broken down in the body, with 90 percent of the compound being released through the urine within 24 hours.¹² Consequently, it does not act as a cure for pre-eclampsia, but rather as a treatment for eclampsia during individual births. It is currently being studied for use as a prophylactic.

In multiple studies including the Magpie Trials, there were no attributable deaths found in women who were administered the drug. The risk that magnesium sulfate poses to infants is likewise minimal.^{13,14} There are a few minor side effects for women. About a quarter of women administered magnesium sulfate experienced headaches, nausea or vomiting, muscle weakness, or respiratory

issues.¹⁵ However, there is a general consensus that the side effects of using magnesium sulfate are negligible in comparison with the enormous benefit it has for at-risk women.

Current program/sector use

Magnesium sulfate has been on the World Health Organization's essential medicines list since 1996 and is highly affordable (a typical dosage costs US\$0.35 per ampoule).¹⁶ However, magnesium sulfate has not achieved widespread usage in developing countries. This is due to lack of public awareness of the drug, lack of adequate service-provider training, and lack of availability of magnesium sulfate in these areas.^{10,17} Its use is relatively widespread in the United States and Europe, having been used to treat severe pre-eclampsia and eclampsia in the United States throughout the 20th century.¹⁸ Use of magnesium sulfate was for many years less common in Europe due to a general perception that it was undesirable compared with more common, multipurpose anticonvulsants such as Diazepam and Phenytoin. However, since the Magpie Trials, there is general international consensus that magnesium sulfate is the drug of choice to treat eclampsia.¹⁹

Manufacturers

The primary manufacturer of magnesium sulfate is Hospira, Inc. (www.hospira.com). The drug (liquid format) is encapsulated in Hospira's Ansyr[®] Single-Dose Plastic Syringe containers at varying doses (2.5g/5ml and 5g/10ml.)

Magnesium sulfate is rarely globally manufactured because its low cost leaves little profit-based incentive for pharmaceutical companies to produce it.²⁰ For service providers or distributors to acquire magnesium sulfate, it is advisable to contact the local Ministry of Health and local pharmaceutical companies (or comparable entities) for information on how to do so.

As of January 2012, WHO regulatory authorities had not yet prequalified manufacturers of magnesium sulfate. It was, however, placed on their 2010 Expression of Interest list as a drug for which they will accept requests for prequalification.

Public-sector price agreements

There are no existing global public-sector price agreements for magnesium sulfate. Depending on the country, however, price agreements may exist between domestic pharmaceutical companies and their governments. For example, the South African government has set a price of US\$5.76 per pack of ten doses of magnesium sulfate.

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Manual vacuum aspiration

Description

Manual vacuum aspiration (MVA) can be used to manage a number of maternal health conditions—such as incomplete and spontaneous abortion or unsuccessful medical abortion—and can be used to perform first-trimester induced abortions and endometrial biopsies. MVA allows for evacuation of the uterus using a hand-held plastic aspirator attached to a cannula (a thin tube). Unlike electric suction, the suction used for uterine evacuation is created manually by extending the plunger of the syringe-like aspirator. MVA is similar to electric vacuum aspiration (EVA). The two methods share a mechanism of action—using suction as the force to remove uterine contents via the cannula. However, for EVA, a large electric machine generates the suction, and the aspiration is performed using a long tube connected to the EVA machine. The need for electricity, the larger size, and the greater cost of the machine precludes the use of EVA in many parts of the world, whereas MVA can be used in any location where basic medical care is provided.

MVA is safe, effective, easy to use, portable, and reusable. It is appropriate for use in many different clinical settings (including developing-country outpatient centers), does not require lengthy training for proper operation, and has yielded both high patient and provider satisfaction.^{1,2} Additionally, there is substantial evidence that mid-level providers—for example, midwives, clinical officers, nurse practitioners, physician assistants—can perform MVA procedures safely and effectively in a range of health care settings.^{3,4}

Efficacy

MVA has been demonstrated to be effective and very safe through clinical studies over the last 30 years. The World Health Organization (WHO) recommends MVA as a preferred method of uterine evacuation.² When compared to sharp curettage (also known as dilation and curettage or D&C), MVA is a safer, more readily

accessible, and potentially less expensive way to offer high-quality services to women.⁵

Studies demonstrate that the efficacy of MVA is comparable to EVA and is successful in approximately 99 percent of cases for early-elective abortion and management of early pregnancy loss. Studies show that 98 percent of vacuum aspiration procedures occur without complications, much higher than the alternative D&C method, which may induce incidences of excessive blood loss, pelvic infection, cervical injury, and uterine perforation.⁶

Current program/sector use

Vacuum aspiration, both electric and manual, is used for about 97 percent of first trimester surgical-induced abortions in the United States. The United Kingdom, Canada, China, New Zealand, Singapore, and other countries use vacuum aspiration for most of their first trimester surgical-induced abortions.⁷ In many developing countries, such as Bangladesh and Vietnam, MVA has been used for several decades to provide early-induced abortion, including procedures referred to as “menstrual regulation.” MVA is well-suited for use in conjunction with medical abortion* if there is a concern that the uterus has not been completely evacuated.

Manufacturer/supplier

MVA is available in many countries. Many governments have identified MVA in clinical guidelines as the preferred method for uterine evacuation. Inclusion in clinical guidelines also helps to ensure adequate and reliable supplies of MVA instruments in their public health systems.

The original MVA device was developed by Ipas—an international organization that works to increase

* For more information on medical abortion, please see the Caucus’ Medical Abortion brief.

women's ability to exercise their sexual and reproductive rights, and to reduce abortion-related deaths and injuries. WomanCare Global (WCG) is the exclusive distributor of Ipas MVA instruments (single- and double-valve aspirators), which are CE marked and manufactured in Taiwan. WCG adheres to ISO 13485 quality standards, audits their manufacturers, and has conducted verification testing for compliance. WomanCare Global provides access to reproductive health products in both the public and private sectors in more than 100 countries.

Marie Stopes International (MSI) has manufacturers in China, Malaysia, and Taiwan who manufacture both single- and double-valve MVA. Both possess the CE mark. MSI is a global non-profit organization providing the full spectrum of reproductive health care in both developing and developed countries.

Currently, there are a number of other MVA products available from other manufacturers, but quality can be variable. Some efforts have been made to assess and document their relative quality.⁸

Registration status

Ipas MVA products are registered by WomanCare Global in countries throughout the world as accepted clinical procedures and approved medical devices.

MSI's MVA products are currently mainly used in MSI clinics, but they are available to external procurers. The CE marking on MSI's MVA products is sufficient for the countries where it operates, so individual country registrations are not required.

Public-sector price agreements

There are no known public-sector pricing agreements at this time.

Procurers are encouraged to contact WomanCare Global (customerservice@womancareglobal.org) for Ipas MVA instruments or Marie Stopes International (orders@mariestopes.org) for MSI MVA instruments.

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Medical Abortion

Description

Medical abortion (MA) is a nonsurgical procedure in which drugs are used to induce abortion. The most effective and safest medical abortion regimen requires the use of two medications: mifepristone and misoprostol. Mifepristone blocks the action of progesterone to enhance the contractility of the uterus and prompt the detachment of the implanted embryo. Misoprostol stimulates strong contractions of the uterus, expelling the products of conception. This process is very similar to that of a spontaneous abortion or miscarriage.¹ Repeated administration of misoprostol alone can also be used to induce abortion. Both drugs also soften and dilate the cervix.

Quality abortion care should include counseling, confirmation of intra-uterine pregnancy, and estimation of length of gestation by the patient's history, bimanual exam, or with ultrasound—although the latter is not required. Family planning and contraception counseling should be provided at the time of the abortion or afterwards. Medical abortion options have made abortion more available to women in a variety of health care settings, and home administration of medical abortion is also highly acceptable.²

Efficacy

The International Federation of Obstetrics and Gynaecology (FIGO) published revised guidelines for the use of mifepristone and misoprostol for MA up to nine weeks, 9–12 weeks, and after 12 weeks gestation in December 2011.³ All the regimens use 200 mg of mifepristone followed by 800 µg of misoprostol administered vaginally, buccally, or sublingually. The misoprostol is taken 24–48 hours after mifepristone up to 9 weeks gestational age or 36–48 hours from 9–12 weeks and after 12 weeks gestational age. Additional doses of 400 µg misoprostol may be required depending on gestational age. These combinations result in complete abortion in more than 95 percent of cases;

the rate of continuing pregnancy is less than 1 percent in gestations up to 63 days' amenorrhea.

Even though the combined regimen of mifepristone followed by misoprostol is significantly more effective than use of misoprostol-alone for early medical abortion,⁴ misoprostol is generally more widely available than mifepristone and has been used alone safely and successfully for medical abortion around the world.⁵ Complete abortion rates with misoprostol-only regimens range from 76 to 96 percent, according to existing research.^{4,6,7}

The use of mifepristone and misoprostol is very safe; medical abortion has not been associated with long-term health impacts and is statistically less risky than continuation of pregnancy.⁸ Medical abortion may be preferable to surgical abortion for some women and their providers, as medical abortion is less invasive and can be perceived to be a more private procedure by some women.

Current program/sector use

There are a number of political, logistical, cultural, religious, financial, and other barriers that limit universal access to medical abortion. Elective abortion is legally restricted in many countries, but almost all countries have provisions under which abortion is legal, including to save the woman's life, preserve physical or mental health, when the pregnancy is a result of rape or incest, or on socioeconomic grounds. Where abortion is legal, challenges may arise in terms of health-system restrictions on where the services can be provided, procurement of the drugs, and provider training to properly inform and counsel patients about their options. However, medical abortion is being made available to women in numerous countries, including some sub-Saharan African countries. The level of use in developed countries such as the United States and those in Europe suggests that women appreciate having an alternative to surgical abortion; women in Europe have

been using mifepristone and misoprostol for more than 20 years.

Manufacturer/supplier

Mifepristone and misoprostol are available from generic manufacturers, as individually-packaged medicines and in combination packs made specifically for MA. There are numerous manufacturers of all three products (mifepristone, misoprostol, and combination packs).

Mifepristone

Two branded generics of mifepristone, Mifeprex (Danco Laboratories) and Mifegyne (Laboratoire Exelgyne), and a non-branded generic (Linepharma), are available in mostly high-income countries. Many more branded and non-branded generic versions of mifepristone are made by numerous pharmaceutical companies in low- and middle-income countries such as India and China, but their export capacity is limited.

Misoprostol

More than 50 branded and non-branded generic versions of misoprostol are manufactured by pharmaceutical companies in high-, middle-, and low-income countries including India, Bangladesh, Brazil, Egypt, China, Peru, South Korea, Chile, Argentina, Mexico, the United States, France, and Russia.⁹ Some of these manufacturers are making products for export to low- and middle-income countries, but, as with mifepristone, many only make products for their local markets. Cytotec® (Pfizer), registered in more than 80 countries, is the most widely available misoprostol product. Gymiso® (HRA Pharma) is another brand-name misoprostol product, though it is currently only available in France.

Mifepristone-misoprostol combination packs

Combination packs containing one tablet of mifepristone (200mg) and four tablets of misoprostol (200 µg each) are currently only made by manufacturers in low- and middle-income countries. Most of these products are made in India and China and are for use in the local market only. However, Medabon®, a combination pack manufactured by Sun Pharmaceuticals, is available for export.* Other manufacturers are also planning to export combination packs as interest grows globally.

In May 2010, misoprostol and mifepristone became eligible for the WHO's Prequalification of Medicines Programme, and efforts are underway to support applications from generic manufacturers of misoprostol.¹⁰

Registration status

Registration of the drugs used for MA is often difficult in many countries, due to political sensitivities and a lack of awareness among policy makers. For example, misoprostol products are registered in most countries around the world, but in a large number of those countries the most commonly available product (Cytotec®) is only registered for the treatment and prevention of gastric ulcers. This is despite a breadth of existing evidence supporting misoprostol's effectiveness for a number of obstetric indications, including MA.[†] In 2005, the combination of mifepristone and misoprostol for MA was included on the World Health Organization (WHO) Model List of Essential Medicines for termination of pregnancy where legal and acceptable, up to 9 weeks of gestation.¹¹ A number of international organizations are working with policy makers and health care officials to ensure both drugs are registered for the breadth of uses for which they are effective, including MA. The information below highlights the global registration status for each drug and the combination pack.

Mifepristone

Mifepristone has been registered and approved for use in medical abortion in 50 countries worldwide; the low-income countries where mifepristone is currently registered are Cambodia, Ghana, India, Mozambique, Nepal, Vietnam, and Zambia.¹²

Misoprostol

As noted above, registration of misoprostol for MA is far from universal. Misoprostol products have only been approved for MA in a few countries, including Ethiopia and Ghana.^{‡,13} Misoprostol has been registered specifically for use with mifepristone for pregnancy termination in France (registered by HRA Pharma as Gymiso®) and Russia (registered by Pentcroft Pharma as Misoprostol).

Mifepristone-misoprostol combination packs

Medabon® is the only product currently registered for medical abortion in Bangladesh, Cambodia, Ghana, India, Nepal, and Zambia. Efforts are underway to register combination packs from other manufacturers in several other countries in sub-Saharan Africa. In India, many brands of Indian-made combination packs are registered for MA, but they are not available for export.

Public-sector price agreements

The Concept Foundation has negotiated a preferential price for public-sector procurement of Medabon® in developing countries. Overall, the number of

* For more information, see Concept Foundation website at www.conceptfoundation.org and www.medabon.info.

† The International Journal of Gynecology & Obstetrics 2007, Volume 99, Supplement 2, contains a series of articles on misoprostol for obstetric indications.

‡ For more information on misoprostol use for obstetric indications in addition to medical abortion, please see the Caucus' brief New and Underused RH Technologies brief on Misoprostol.

manufacturers for these drugs is large, and the market is continuing to evolve. Pricing varies by manufacturer, is country-specific, and is often dependent upon product demand.

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Misoprostol for maternal health

Description

Misoprostol can be used for a number of obstetric indications that address maternal health concerns. Misoprostol acts as a uterotonic by stimulating strong contractions of the uterus and also softens and dilates the cervix, similar to the natural process of labor. Its uses related to maternal health are many and include the prevention and treatment of postpartum hemorrhage, labor induction, treatment of incomplete abortion and miscarriage, induced abortion, treatment of missed abortion, treatment of intrauterine fetal death, and cervical ripening.

Dosing regimens vary depending on the medical indication. For labor induction and cervical ripening, the dose can be as low as 25 µg; however, the other indications require a dose of between 400–800 µg. Recommended routes of administration are oral, sublingual, rectal, or vaginal. Dosage guidelines for all indications listed above have been issued by the International Federation of Gynecology and Obstetrics (FIGO).¹ See also <http://www.misoprostol.org>. Misoprostol is available in tablet form, and marketed products typically have a shelf life of 18–36 months when stored below 25–30°C (77–86°F) in a dry area.

Efficacy

For the prevention of postpartum hemorrhage (PPH): Misoprostol is an effective alternative uterotonic, where use of oxytocin or other injectable uterotonics requiring refrigeration and administration by a skilled provider is not feasible. For these reasons, misoprostol can be especially useful in home deliveries. In a multi-center study conducted in hospitals, oxytocin performed marginally better than oral misoprostol in controlling

blood loss.² In a study of women delivering at home in India, oral misoprostol was associated with a significant reduction in the rate of acute postpartum hemorrhage compared to women not using a uterotonic.³ A significant reduction in PPH was also observed with oral misoprostol when administered by traditional birth attendants during home deliveries in Pakistan.⁴

In 2000, the World Health Organization (WHO) recommended the prophylactic use of a uterotonic immediately after delivery for all women, as part of the active management of the third stage of labor,⁵ and oxytocin is recommended as the first line drug. In March 2011, the WHO included the use of 600 µg oral misoprostol for prevention of PPH in the 17th Model List of Essential Medicines.⁶

For the treatment of PPH: In women who were given prophylactic oxytocin as part of the active management of the third stage of labor, misoprostol and oxytocin were found to be clinically equivalent when used to stop excessive post-partum bleeding.⁷ In women not exposed to prophylactic oxytocin, although oxytocin was found to be more effective at controlling bleeding within 20 minutes, researchers concluded that 800 µg sublingual misoprostol might be a suitable first-line treatment in settings in which use of oxytocin is not feasible.⁸

For the treatment of incomplete abortion and miscarriage: The efficacy of misoprostol to treat incomplete abortion and miscarriage is between 91 to 99 percent, equivalent to the use of manual vacuum aspiration.* Medical management of incomplete abortion and miscarriage with misoprostol provides a good opportunity to scale up post-abortion care services.† Use of 600 µg oral misoprostol for this indication was included in the WHO 16th Model List of Essential Medicines in 2009 and in the WHO Priority Medicines for Mothers and Children issued in 2011.^{7,9}

* For a complete list of references and discussion, please refer to the medial Post-abortion care (PAC) toolkit located at www.vsinnovations.org/resources.html or www.ipas.org/ma/mpactoolkit.

† Further information on the treatment of incomplete abortion with misoprostol and service delivery guidelines for integrating misoprostol into PAC services can be found at <http://vsinnovations.org/resources.html> or <http://www.ipas.org/ma/mpactoolkit> and <http://gynuity.org/resources/info/guidebook-on-misoprostol-for-treatment-of-incomplete-abortion/>.

For induced abortion[‡]: Effectiveness of misoprostol-alone regimens for early-term medical abortion range from 76 to 96 percent. Even though it is not as effective as the combination of mifepristone and misoprostol, misoprostol is more widely available than mifepristone and has been used safely and successfully for medical abortion around the world.¹⁰

For labor induction: Cochrane Reviews have concluded that oral misoprostol is more effective than placebo and at least as effective as vaginal dinoprostone for induction of labor with doses not exceeding 50 µg;¹¹ similarly, while vaginal misoprostol is more effective than other conventional methods, low dose oral misoprostol is preferable.¹² In 2011, the WHO recommended the use of both oral (25 µg, two-hourly) or vaginal (25 µg, six-hourly) misoprostol for the induction of labor.¹³

Current program/sector use

In the developed-world setting, misoprostol is used off-label for many of its clinical indications, including induction of labor and cervical ripening, and in combination with mifepristone for medical abortion, where legally permissible.¹⁴

In developing countries, programs to introduce misoprostol into the health system for a variety of obstetric indications are being implemented. For the prevention of PPH, pregnant women have been taught to self-administer 600 µg misoprostol tablets orally as soon as their baby is delivered. Studies in Afghanistan,¹⁵ Nepal,¹⁶ and Bangladesh¹⁷ show that women can use misoprostol consistently and safely (even for twin deliveries) when the drug is distributed by community health workers to women planning to deliver at home. Programs in Ethiopia, Kenya, Tanzania,¹⁸ Mozambique, Zambia, Bangladesh, Uganda, Nigeria, and Senegal have shown that distribution at antenatal-care checks and through community health workers is effective and that misoprostol is used safely and correctly at home deliveries. Some countries are now taking steps to scale up the use of misoprostol in national safe motherhood programs and are also including the use of misoprostol for treatment of incomplete abortion and miscarriage in post-abortion care programs.

Manufacturer/supplier

More than 50 branded and non-branded generic versions of 200 mg misoprostol tablets are manufactured by pharmaceutical companies in high-, middle-, and low-income countries including India, Bangladesh,

Brazil, Egypt, China, Peru, South Korea, Chile, Argentina, Mexico, the United States, France, and Russia.¹⁹ Some of these manufacturers are making products for export to low- and middle-income countries, but many only make products for their local markets. Cytotec[®] (manufactured by Pfizer) is the most widely available misoprostol product. There are few manufacturers of the 25 mg tablet. As of May 2010, misoprostol became eligible for the WHO's Prequalification of Medicines Programme,²⁰ and efforts are underway to support applications from generic manufacturers of misoprostol.

Registration status

Registration, or market approval of a drug by a country's drug regulatory agency, grants permission for a product from a specific manufacturer to be marketed in that country by a pharmaceutical distributor for the medical indications for which the application was made. The registration status of misoprostol varies. It is often only registered for some of its many obstetric indications, while in many countries it is not registered for these indications at all. For example, misoprostol is most commonly registered for prevention and treatment of gastric ulcers; Cytotec[®], is registered in more than 80 countries but only for these two indications. As noted previously, in many countries misoprostol may be legally used for off-label indications.

Misoprostol is increasingly being registered for obstetric indications. A limited number of manufacturers make misoprostol for export. Exporting manufacturers that have registered products for obstetric indications include Acme Formulations, Cipla, Sigma Pharmaceuticals, Square Pharmaceuticals, and Zizhu Pharmaceutical, and there are likely to be others.

Products are registered for obstetric indications in more than 15 countries, including Bangladesh, Bolivia, India, Ethiopia, Kenya, Malawi, Mali, Mozambique, Myanmar, Nepal, Pakistan, Senegal, Sudan, Somaliland, Tanzania, Uganda, and Zambia. More registrations are expected in the coming years as interest in misoprostol grows. The approved indications vary across countries; in some countries, products are only registered for PPH prevention and treatment, while in others they are registered for multiple obstetric indications. The indications for which the drug is granted approval usually depend on the level of commitment and willingness of governments to integrate misoprostol into safe motherhood programs. More information on the global status of misoprostol registration can be found at <http://www.vsinnovations.org/resources.html>.

[‡] For more information on misoprostol for induced medical abortion, please see the Caucus on New and Underused RH Technologies brief on Medical Abortion.

Public-sector price agreements

There are no global public-sector price agreements for misoprostol. Governments can purchase a misoprostol product that is registered in their country and can negotiate the price with the distributor that holds the market approval.

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Oxytocin brief

Description

Oxytocin is a peptide hormone best known for its roles in childbirth and breastfeeding. It is released in large amounts from the body's pituitary gland during labor, causing contractions of the uterus to facilitate birth. It also stimulates contractions during the third stage of labor—separation of the placenta from the uterine wall and compression of maternal blood vessels after delivery of the placenta.¹ When uterine contractions are not strong enough to compress blood vessels, postpartum hemorrhage (PPH) can threaten a woman's life. In this situation, a woman will be given a uterotonic medicine, such as oxytocin or ergometrine, to stimulate contractions and stop the bleeding.*

Obstetric hemorrhage is estimated to cause 25 percent of all maternal deaths and is the leading direct cause of maternal mortality worldwide.² In Africa and Asia, nearly a third of pregnancy-related deaths are associated with PPH.^{3,4} The World Health Organization (WHO)⁵ and other international bodies⁶ recommend active management of the third stage of labor (AMTSL) to prevent severe bleeding after childbirth. This includes administration of a uterotonic soon after birth of the baby, delayed cord clamping, and delivery of the placenta by controlled cord traction and uterine massage.⁵

According to the WHO, oxytocin is the preferred drug for prevention and initial treatment of PPH because it is effective in two to three minutes after injection, can be used in all women, and is more stable in storage than ergometrine.⁷ WHO, with the Partnership for Maternal, Newborn, and Child Health, lists oxytocin as a first-line drug for induction of labor, AMTSL, and the prevention and management of PPH.⁸ The United Nations Population Fund (UNFPA) and its partners have identified oxytocin as one of four priority medicines that

can save mothers' lives during difficult pregnancies and childbirth.⁹

The standard dose of oxytocin for preventing PPH is ten international units (IU) administered intramuscularly within a few minutes after birth. If a woman is experiencing heavy bleeding after delivery and the initial intramuscular dose of oxytocin, the WHO recommends an intravenous (IV) line be inserted and the woman given 20- to 40-IU oxytocin in one liter of IV fluid at 60 drops per minute, and that oxytocin infusion be continued at 20 IU in one liter of IV fluid at 40 drops per minute until hemorrhage stops.¹⁰ Oxytocin is most commonly available in either 5- or 10-IU glass ampoules.

Efficacy

WHO has determined that, as a package, AMTSL can reduce PPH by as much as 60 percent.¹¹ WHO also reviewed the available evidence for using oxytocics for treatment of PPH, and while both oxytocin and ergometrine were similarly effective, ergometrine is associated with more adverse effects, especially vomiting and high blood pressure.¹¹

Current program/sector use

Oxytocin is used worldwide for several indications. As noted above, it is the WHO preferred uterotonic for prevention and treatment of PPH and it is also used to induce and augment labor. In some developed countries it is used to initiate or increase breast milk production.

In developing countries, oxytocin is commonly used in clinical environments where a skilled birth attendant and refrigeration are available. However, utilization of oxytocin for the indications noted previously is not universal and other drugs are also being used for

* If oxytocin or ergometrine are unavailable, or bleeding continues despite the administration of one of these drugs, the WHO recommends women be given a prostaglandin such as misoprostol. Please see the Caucus product brief on Misoprostol for more information.

induction and augmentation of labor, and for prevention or treatment of PPH.¹² This is due to a variety of reasons, including changes in recommendations over time; corresponding differences in country-level protocols and guidelines; and differences in the availability, cost, and storage requirements for the various drugs.

Oxytocin in the Uniject^{™**} injection system (oxytocin in Uniject), a pre-filled, single-dose injection system, has successfully been used by skilled providers in health facilities¹³⁻¹⁷ and research on the use of oxytocin in Uniject for the prevention of PPH during home- and community-level deliveries is currently underway in Ghana, Vietnam, India, Senegal, and Mali.

Work is underway to increase access to oxytocin by making it more heat stable and easier to use, particularly for developing-country settings with limited access to skilled birth attendants and refrigeration. A number of organizations are investigating potential improvements to the heat stability of oxytocin, including a consortium made up of the WHO, the International Confederation of Midwives, and pharmaceutical companies, among others.¹⁸ Some of these organizations are also seeking to make oxytocin easier to deliver through non-parenteral routes, such as dry powder inhalation.

Manufacturer/supplier

Oxytocin is a generic drug no longer subject to patent protection, and it is widely produced and distributed around the world. Two oxytocin brand names are broadly recognized: Syntocinon®, which is marketed by Novartis; and Pitocin®, which is marketed by Pfizer in some countries and other producers in other countries. There are multiple generic manufacturers of oxytocin in almost all countries that have an active sterile injectables pharmaceutical manufacturing sector, including India, China, Bangladesh, Argentina, Pakistan, and Indonesia. Two manufacturers, Instituto Biologico Argentino (BIOL) (Argentina) and Gland Pharma (India), are manufacturing oxytocin in Uniject.

As noted above, oxytocin, whether packaged in ampoules or a prefilled injection device such as Uniject[™], is a heat-sensitive product. Depending upon the manufacturer and regulatory agency specification, oxytocin products should be stored at either controlled room temperature (25°C or less) or refrigerated storage (2°–8°C) in order to ensure quality and comply with the labeled storage conditions. There is widespread inconsistency in the labeled storage conditions for oxytocin from various manufacturers, which can lead to confusion about proper storage practices.

Registration status

Oxytocin is often registered for multiple obstetric indications including prevention and treatment of PPH, as well as induction of labor. Due to the large number of manufacturers producing oxytocin globally, a complete listing of all manufacturers and their corresponding country registrations is beyond the scope of this brief; however, almost all countries have one or more registered oxytocin product.

Oxytocin in Uniject is currently registered for commercial sale in Argentina, Bolivia, Ecuador, Guatemala, Honduras, Nicaragua, Paraguay, and Uruguay by BIOL. Modest commercial sales of the product are under way in Argentina. Gland Pharma has registered oxytocin in Uniject for sale in India although it is not actively marketing the product at this time.

Public-sector price agreements

According to the International Drug Price Indicator Guide for prices in 2010,¹⁹ the median cost to procurers of oxytocin (both nonprofits such as UNFPA and for-profit organizations that sell to charitable groups) is US\$0.18 per 10-IU ampoule. The median cost for governments purchasing from agencies such as these is US\$0.24, but the cost can be as low as US\$0.03.

There are no known global public-sector price agreements for oxytocin. Governments can purchase oxytocin products that are registered in their country and can negotiate the price with the distributor that holds the market approval.

Efforts are underway to secure WHO prequalification for oxytocin and oxytocin in Uniject.

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** Uniject is a trademark of BD.

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Progesterone vaginal ring

Description

The progesterone vaginal ring Progering® is used to extend the contraceptive effectiveness of lactational amenorrhea among breastfeeding women. Progesterone vaginal rings are inserted in the vagina for continuous use for up to three months and replaced with a new ring if breastfeeding is continued and extended contraception is desired. Women can use these rings continuously for up to one year. Although not recommended, the ring may be removed during sexual intercourse for a period of up to two hours. If the ring is removed for a longer period of time, an additional contraceptive method should be used for the following seven days. Upon weaning of the breastfeeding infant, progesterone rings should be replaced with another effective method if continued contraception is desired.¹

The progesterone vaginal ring functions by diffusing a continuous flow of progesterone through the vaginal walls—approximately 10mg per day—which then enters the bloodstream and regulates the woman's fertility by suppressing ovulation. Progesterone also thickens the cervical mucus, inhibiting sperm penetration into the uterus.

Progesterone vaginal rings have a noteworthy presence in today's contraceptive method mix, especially as a contraceptive choice for breastfeeding women. Acceptability studies conducted with other contraceptive rings in Australia, Canada, Chile, the Dominican Republic, the United States, and Europe have demonstrated that women generally like the vaginal ring for many reasons, including its effectiveness; its ease of use, including insertion and removal; the user control of these actions; and the lack of need to check it regularly.²

Efficacy

Clinical trials have shown a high contraceptive efficacy (over 98.5 percent) and a good safety profile. There have been some sideeffect reports of vaginal discharge, urinary discomfort, bleeding disturbances, and rare reproductive tract infections. In a Chilean study, less than 5 percent of users experienced any one of these side effects.³

The effectiveness of the progesterone ring during the recommended three months of use has been shown to be comparable to that of the Copper T-380A intrauterine device. While progesterone rings are less effective overall than rings containing both a progestin and an estrogen, they are highly effective among breastfeeding women because exclusive breastfeeding itself provides some protection from pregnancy. Also, they are more appropriate for use by breastfeeding women because they do not contain estrogen, which can reduce milk production. The most common reason for discontinuation of progesterone rings is weaning, as mothers choose more effective contraception after they reduce breastfeeding episodes. Bleeding disturbances, a common side effect of all progesterone-only methods, is another frequent reason for discontinuation.³ The progesterone ring does not provide protection from sexually transmitted infections, including HIV.

Current program/sector use

The product Progering® is sold commercially in six countries in Latin America through gynaecologists. There is limited data on commercial sales in these countries and available information suggests that market penetration is weak.

Further clinical trials and social research are also being conducted on this product in India, in anticipation of its registration and commercialization there once approved by the Drug Controller of India. Further acceptability studies will be conducted in three countries in sub-Saharan Africa prior to introduction in these markets.

Manufacturer

Progering® is the brand name of the progesterone vaginal ring currently available in Latin America for contraceptive use and is manufactured by Laboratorios Andromaco SA in Chile. The product is supplied by Laboratorios Andromaco.

Registration status

Progering® was registered in Chile and Peru in 1998 for use by breastfeeding women. It was approved and launched in 2010 in other countries in Latin America including Bolivia, Chile, Ecuador, Guatemala, Honduras,

and Peru. The Population Council, CONRAD, and the private companies Silesia SA and Andromaco SA funded its development.

Public-sector price agreements

None.

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