APPLICATION

Progestosterone contraceptive vaginal ring for use during breastfeeding

SUBMITTED TO
World Health Organization (WHO)

OBJECTIVE
Application for inclusion of the Progestosterone Contraceptive Vaginal Ring in the WHO Model List of Essential Medicines

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GENERAL ITEMS

1. Summary statement of the proposal for inclusion

Here within, please find the evidence to support the inclusion of the Progesterone Contraceptive Vaginal Ring (PCVR) for breastfeeding women in the World Health Organization’s Essential Medicines List (EML). Globally, over 65% of women in their first postpartum year express an unmet need for family planning. Developing countries have disproportionately high levels of unmet need for contraception compared to other regions of the world. In order to address some of the barriers to effective contraception, there is renewed focus on new methods that offer greater ease of use, especially in terms of not requiring daily action, are women-controlled, and do not require medical providers and significant health system infrastructure for service delivery. The PCVR holds great potential in offering a safe, effective and easy-to-use family planning method for breastfeeding women (RamaRao et al. 2013). Currently, there are no progesterone contraceptive vaginal rings on the EML.

The clinical indication for the PCVR is contraception during breastfeeding. The target population for this method is women of reproductive age, from 4 weeks up to one year postpartum who are actively breastfeeding at least 4 times per day. Existing progestin-only contraception (POCs) used during lactation include mostly synthetic progestin and are not considered harmful to infants from exposure through breast milk (WHO MEC 4th Edition 2009). The natural progesterone delivered through this vaginal ring is similar to the hormone secreted by the mother when ovulating.

The PCVR is a contraceptive method offering many advantages. As mentioned above, it contains the natural progesterone hormone. When given orally the hormone is rapidly degraded and if a small amount reaches the infant via the mother’s milk, it is quickly inactivated. Also progesterone systemic levels remain low contrary to other POCs which are administered orally and have a prolonged half-life. It can be vaginally inserted and removed by the user without professional assistance except for the examination and instructions provided when initiating the method. In addition, the method does not require cold chain storage or specialized facilities. Finally, its use does not interfere with the production of milk, growth of the child or the health of the mother and child. Moreover, because this method is effective for women who breastfeed at least 4 times per day during use, it extends the period of amenorrhea during lactation thereby promoting breastfeeding with its attendant benefits to the newborn (Progering® Monograph 2004; Brache and Faundes 2010).

A systematic review comparing the PCVR versus other methods is being finalized at WHO RHR and has been evaluated using GRADE as part of the update for the revised WHO Contraceptive Guidelines. See Appendix I for GRADE table prepared by WHO RHR.

2. Name of the focal point in WHO submitting or supporting the application

Department of Reproductive Health and Research (RHR)

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Contacts:
Dr. Mario Festin        Dr. Mary Lyn Gaffield
festinma@who.int    gaffieldm@who.int

4. International Nonproprietary Name (INN, generic name) of the medicine

**Generic name:** Progesterone (pregn-4-ene-3, 20-dione; abbreviated as P4, or P). The PCVR delivers 10mg of P per day via a 3-month vaginal ring.

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

The formulation proposed for inclusion is Progesterone (pregn-4-ene-3, 20-dione; abbreviated as P4 or P) delivered at 10mg of P per day via a 3-month vaginal ring. This formulation is applicable only to reproductive-aged women who are breastfeeding from 4 weeks postpartum and up to one year. Women below 18 years of age have not been included in clinical trials. However, as females less than 18 years of age who become pregnant would have the same hormone levels as those over 18 years; it is unlikely that specific risks exist for females age 18 and under. Females under 18 years who have already had 1 or more children may benefit from use of this product to promote child spacing and enhance overall maternal-infant health.

6. International availability - sources, of possible manufacturers and trade names

This formulation is manufactured in Chile by Grupo Grünenthal Chile, Avenida Quilin N° 5273Peñalolen, 7931398, Santiago, Chile.

The product is registered under the brand name Progering® in 8 countries in Latin America: Bolivia, Chile, Dominican Republic, Ecuador, El Salvador, Guatemala, Panama, and Peru. Submissions for regulatory approval in Columbia, Honduras and Paraguay are either complete or nearly complete. Submissions for regulatory approval are currently being prepared for Brazil and Mexico.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

The PCVR is an individual medicine (device delivering an active hormone). Although the natural hormone progesterone is the lead hormone of the progestin class, it differs from the synthetic progestin used as POCs in this indication. However all these progestogenic hormones act by binding to the same progesterone receptors (PRs) [PCVR Investigator’s Brochure (IB) 2008].

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Globally, about 222 million women aged 15 to 49 have an unmet need for modern family planning (FP) methods (Singh and Darroch 2012). Over 65 percent of women in their first postpartum year, especially in developing countries are included in this group. According to an analysis of Demographic and Health Surveys data from 27 countries, 95 percent of women who are as much as 12 months postpartum want to avoid a pregnancy within the following 24 months, but 70 percent do not use contraception (Ross and Winfrey 2001 in Obare et al. 2014). While part of the challenge is women’s limited use of contraception during their first six to 12 months postpartum, high discontinuation rates constitute another element, with about half of all users abandoning their methods within six months of first adoption (Ali et al. 2012, Bradley et al. 2009, Gebreselassie et al. 2008 in Obare et al. 2014). Non-use and discontinuation of contraception lead to limited success in effective birth spacing and a high incidence of unwanted pregnancies, unsafe abortions, unplanned pregnancies, poor infant health, and maternal mortality. Postpartum family planning could prevent an estimated 30 percent and 10 percent of maternal and child mortalities, respectively (Cleland et al. 2006 in Obare et al. 2014).

While there is clearly a need for contraceptive options in the postpartum period, few choices exist for breastfeeding women. Currently IUDs, implants containing progestins and injectable contraceptives are suitable for postpartum women but they require a skilled healthcare provider, often limiting access and use in many developing countries. The Progesterone Contraceptive Vaginal Ring (PCVR) is a method that offers effective contraception to breastfeeding women that is safe for both mothers and babies. After an initial examination and orientation to the method by a healthcare provider, the woman can insert and remove the ring herself in private, reducing the need for frequent visits to the provider. When a woman initiates use, there should be adequate and appropriate counselling on use including hygiene and slippage. After this first consultation the woman can control the use of the method herself, however, she should be instructed to contact a healthcare provider if she experiences
any discomfort. Subsequent vaginal rings can be made available by low and mid-level health care providers, community health workers and pharmacists.

The woman-initiated nature of the PCVR is important, especially in settings with resource constraints or where a woman’s autonomy to seek care independently or her mobility is limited. Many developing countries experience provider shortages or service delivery challenges such as lack of counselling materials and clinical supplies that affect access to methods. Further, a product that can be initiated and withdrawn by women is valuable in settings where women are disempowered in their relations with their partner, family or provider. Women like the greater control over the use of the ring because it makes them less dependent on health providers (Sanchez 1997). In an ongoing trial in India comparing the PCVR and Copper T IUD, women cited user control as the attribute they liked most about the PCVR (personal communication with study principal investigator (PI); data presented at the International Committee on Contraception Research (ICCR) meeting October 2014). In one comparative study of the PCVR and the IUD in Chile, control over the ring was associated with property, responsibility, and autonomy (Sanchez 1997).

In a review of the literature on the acceptability of various vaginal ring technologies on the market (i.e., two for contraception, one for progesterone supplementation, and two for estrogen therapy), as well as rings in development (for contraception and HIV prevention) the evidence suggests that women generally find vaginal ring technologies acceptable and easy to use. Despite some cases of ring slippage and expulsions, health effects such as vaginal discharge, and feeling the ring during intercourse, women report being satisfied with the ring and would recommend it to others (Merkatz et al. 2014). In regards to the PCVR in particular, women liked that it contains a natural hormone, is easy to use, and is user-controlled (Preliminary results of willingness to participate study). Although data regarding how partners feel about vaginal rings are limited, the evidence we do have suggests that male partners support its use (Sanchez 1997). Some partners may feel the ring during intercourse, however; this does not necessarily deter support for using the PCVR.

The target population for the PCVR is postpartum women in the first year after delivery and who are breastfeeding at least four times per day.

9. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)**

**Indication:** Progesterone Contraceptive Vaginal Ring (PCVR) for use during breastfeeding.

The PCVR has been developed as a doughnut-shaped device composed of a soft flexible silicone elastomer; progesterone is dispersed throughout the ring. It is comprised of a silicon elastomer in which 2 grams of progesterone is homogenously dispersed [22.5% (w/w)]; the external diameter and its cross-sectional diameter are 58mm and 8.4mm, respectively. The ring releases progesterone at an average daily rate of 10 mg during 3 months of continuous use; therefore the ring must be renewed every 3 months. In a previous pharmacokinetic study, a maximum mean progesterone plasma concentration, 33.7 ± 2.5 nmol/L (10.6 ± 0.8 ng/mL), was reached during week 1; mean progesterone plasma concentration declined to approximately 25 nmol/L (7.9 ng/mL), 17 nmol/L (5.4 ng/mL), and 10 nmol/L (3.1 ng/mL) in weeks 4, 9, and 16, respectively (Massai 1999; IB 2008). The mechanism of action is based on the inhibition of ovulation in nursing women (Diaz et al. 1991).
The PCVR is indicated from 4 weeks postpartum up to one year, in women who are actively breastfeeding at least 4 times a day. One vaginal ring is recommended for use for 90 days with an additional 10 day allowance (Progering® Monograph 2004) and a multicentre study showed that up to 4 rings used consecutively for one year were able to prolong lactational amenorrhea and prevent pregnancy similarly to an intrauterine device (IUD) (Sivin et al 1997). The PCVR may be removed for up to 2 hours at a time and reinserted after washing with soap and water. If removed for greater than two hours, the woman may be at risk of ovulation and pregnancy. Therefore she will be instructed to use condoms for 3 to 4 days as a back-up method together with the reinserted PCVR. Alternatively, she may choose to switch to another method. In case the ring has been removed for several days, a pregnancy test should be conducted before using another method. In cases where the ring is expelled or if it slips out of place, the woman is instructed to reinsert it herself.

There is no need for a cold chain for distribution or storage, special diagnostics, equipment, treatment facilities or skills. It can be introduced through primary health care settings. Since a woman inserts and removes the ring herself, knowledgeable health care providers including trained community workers or pharmacists can instruct a woman on its use. No cases of ring breakage have been reported in studies or in post marketing surveillance.

**Contraindications and warnings:** Progesterone is a natural hormone for which there are no contraindications in the doses delivered by the vaginal ring. Nevertheless, hypersensitivity to any of the components of the vehicle, although no cases exist, is considered a contraindication as well the presence of a genital tract infection (e.g., endometritis in the postpartum). In case of infection, the ring should not be used until the infection has been controlled (Progering® Monograph 2004).

In case of dyspareunia, genital actinomycosis, suspected or actual endometrial or cervical neoplastic pathology, recurrent urinary and vaginal infections, an appropriately competent care provider must evaluate if the use of the ring represents an additional risk for each patient. If the vaginal infections occur during use, they must be treated and the healthcare provider must decide if the ring should be removed. In this case, the treatment with a new ring can be reinitiated once the infection is under control. It is recommended to instruct the woman who uses the ring to consult a physician in cases of pain, secretion with bad odor and/or genital injuries (Progering® Monograph 2004).

A review comparing the PCVR compared to other methods is being finalized at WHO RHR and has been evaluated using GRADE as part of the update for the revised WHO Contraceptive Guidelines. See Appendix I for GRADE table prepared by WHO RHR.

The PCVR is being proposed for inclusion in the core list.

**PUBLIC HEALTH NEED AND EVIDENCE APPRAISAL AND SYNTHESIS**

**10. Summary of comparative effectiveness in a variety of clinical settings**

The efficacy of this PCVR has been evaluated in lactating women during clinical trials conducted in Chile, Peru, the Dominican Republic, Egypt, Thailand, China, and Singapore (PCVR IB 2008; See Table 1). Studies are comparative, open label, cohort studies. They are not randomized, blinded, placebo
controlled studies because this gold standard would not allow for a woman to choose which contraceptive method she wishes to use. As there is no comparator to the PCVR, it has been evaluated against IUDs, implants and POPs.

From previous studies and published reports of study results the main findings in **Contraceptive Effectiveness** are as follows: Prior studies have confirmed that the PCVR is similar to the Copper-T 380A IUD in terms of contraceptive effectiveness. A comparative trial of the PCVR and Copper-T 380A IUD which included 802 women (PCVR group) and 734 women (IUD group) was conducted across nine clinics (five in Asia, two in Latin America, one in North Africa and one in the United States). The one year pregnancy rate with the ring was observed to be 1.5 per 100 (431 women-years) which did not differ significantly from 0.5 per 100 in the Copper-T 380A cohort (533 women-years) (Sivin et al 1997). In a Chilean trial which enrolled a total of 285 volunteers to use the ring and 262 to use the Copper-T, no pregnancies were observed in 2320 and 2183 women-months of exposure with the PCVR and Copper-T respectively (Massai et al 1999). In clinical trials with PCVRs delivering 10 mg/day, 3 of 1,466 breastfeeding women became pregnant while using this method during 10,829 woman-months of exposure (PCVR IB 2008).

Studies have shown effectiveness for one year. Women will not be denied if they wish to continue use for longer while continuing breastfeeding; however, they will be told that the method may not be effective beyond one year.

**Table 1*. Progesterone contraceptive vaginal ring for use during lactation: Overview of efficacy and safety**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design, location, duration</th>
<th>Study participants</th>
<th>Efficacy (pregnancies)</th>
<th>Nursing episodes/d Full nursing duration</th>
<th>Infant weight, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivin et al 1997</td>
<td>Comparative: PCVR (replaced every 3 mo) vs CuT380A IUD Multicenter study: Asia (5 clinics); Latin American (2); North Africa (1); USA(1) 12 months</td>
<td>PCVR: 802 CuT380A: 734</td>
<td>6 mo PCVR: 1/100 CuT380A IUD: 0.5/100c 12 mo PVR: 1.5/100 CuT380A: 0.5/100c</td>
<td>Nursing episodes: 6 mo PCVR: 8.3 CuT380A: 7.9 P&lt;0.05 Full nursing duration: 6 mo approximately 1/2 per group</td>
<td>6 mo PCVR: 7805 CuT380A: 7790c</td>
</tr>
</tbody>
</table>
A systematic review comparing the PCVR compared to other methods is being finalized at WHO RHR and has been evaluated using GRADE as part of the update for the revised WHO Contraceptive Guidelines. See Appendix I for GRADE table prepared by WHO RHR.

### 11. Summary of comparative evidence on safety:

The safety of this PCVR has been evaluated in lactating women during clinical trials conducted in Chile, Peru, the Dominican Republic, Egypt, Thailand, China, and Singapore (PCVR IB 2008; See Table 1).

**Safety for mothers:** No serious Adverse Events (AEs) have been reported in women who used progesterone contraceptive vaginal rings in previous clinical trials or in an ongoing trial in India. In addition, Grünenthal has a pharmacovigilance system in place, and to date there have been no reported Serious Adverse Events. Non-serious AEs are not different between groups and mostly relate to hormonal effects of bleeding.

The AEs occurring in previous studies with PCVRs have generally been mild and typical of those reported by women using progestin-only contraceptives. AEs that have occurred are easily controlled and most occur in less than 1% of users. In the largest comparative study conducted to date, vaginal problems, the most frequently occurring AE, were reported by a higher percentage of women using the PCVR than the CuT380A IUD (25.8% vs 16.8%; P < 0.001); however, fewer women using the PCVR than the CuT380A IUD experienced abnormal findings on the vaginal examination (14.8% vs 19.9%, P < 0.01). Abnormal findings on vaginal examination included discharge, vaginitis, mycosis (yeast), trichomonas, other organisms, and “other.” Vaginal discharge was observed more frequently among IUD users. In a preregistration study of the PCVR in Chile, vaginal problems were more frequently reported by users of the PCVR than the CuT380A IUD (3.5 vs 1.9 per 100 woman-months; P = 0.005), but menstrual events were reported less frequently by PCVR users (0.6 vs 1.4 per 100 woman-months; P=0.008) as was low abdominal pain (1.8 vs 3.0 per 100 woman-months; P= 0.009). (See Table 2).
Table 2: Percentages of women who reported specified gynaecological problems or in whom abnormalities were detected during examination

<table>
<thead>
<tr>
<th>Problem</th>
<th>PCVR (Range)</th>
<th>TCu (Range)</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>25.8 (2-37)</td>
<td>16.8 (2-34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>14.3 (7-23)</td>
<td>15.5 (6-29)</td>
<td>NS</td>
</tr>
<tr>
<td>Low-abdominal pain</td>
<td>9.5 (1-24)</td>
<td>17.2 (2-36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breast</td>
<td>3.4 (-12)</td>
<td>3.1 (0-10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abnormal Findings**

| Vaginal                      | 14.8 (1-44)  | 19.9 (0-47) | <0.01 |
| Discharge                    | 9.1          | 13.8        |       |
| Vaginitis                    | 1.8          | 3.0         |       |
| Mycosis, yeast               | 2.7          | 2.7         |       |
| Trichomonas                  | 1.5          | 2.2         |       |
| Other organisms              | 0.1          | 0.1         |       |
| All other vaginal            | 1.5          | 1.9         |       |
| Cervical                     | 1.6 (0-9)    | 3.8 (0-16)  | <0.01 |
| Ectropion                    | 0.6          | 1.4         |       |
| Cervicitis                   | 0.4          | 0.0         |       |
| Erosion/lesion               | 0.2          | 1.6         |       |
| Partial expulsions           | NA           | 1.0         |       |
| Other                        | 0.4          | 0.3         |       |
| Uterine                      | 1.9 (0-4)    | 1.5 (0-3)   | NS    |
| Adnexal                      | 0.4 (0-2)    | 1.9 (0-14)  | <0.01 |
| Breast                       | 4.0 (0-12)   | 4.5 (0-2)   | NS    |
| Cardiovascular               | 0.2 (0-1)    | 0.7 (0-2)   | NS    |
| Other                        | 4.2 (0-13)   | 5.4 (0-13)  | NS    |

Numbers in parentheses represent the ranges among the seven clinics with 25 or more acceptors of each method. NS: not significant

Sivin 1997

Weaning was the most common reason for early termination of PCVR use in these studies. Use problems, including expulsion and removing the PCVR for more than 48 hours, were the second most common reason for early termination. In studies comparing the PCVR and the Copper-T 380A IUD (CuT380A IUD), continuation rates were lower among PCVR users because of use problems, which are expected in a user-controlled method.

In a comparative clinical study in lactating women, bone density in lumbar spine and femoral neck and markers of bone turnover were assessed in 29 women using Norplant implants, 28 using a PVR, and 27 using a CuT380A IUD. Increased bone remodelling was observed during lactation among women using all three methods of contraception. After weaning, all values returned to those observed in non-lactating women. Similarly, no differences were found between groups in any measurement of bone density; bone density in lumbar spine decreased in comparison to that seen in non-breastfeeding women in the first month after delivery; no differences were found among groups after weaning (PCVR IB 2008).

**Breastfeeding and infant growth:** In all clinical studies involving a PCVR, no deleterious effects on the frequency of breastfeeding, breast milk volume, or infant growth have been observed. (Massai 1999, Sivin 1997, Diaz 1997, IB 2008). The progesterone (P) vaginal ring has been found to exert its
contraceptive effect without interfering with breastfeeding performance or infant growth. The circulating level of P which exerts contraceptive effects released by the ring is within the lower half of normal luteal phase values, with the maximum peak being $11.6 \pm 8.0 \, \text{ng/mL}$ during the first week of use, while the level during a normal luteal phase of the menstrual cycle ranges from 8.3 to 25 ng/mL. Average plasma concentrations in PCVR users are reported at 20nmol/L ($\sim 7 \, \text{ng/ml}$) (Progereg® Monograph 2004). The transfer of P to the infants via breast milk of mothers using progesterone subdermal implants was evaluated by measuring urinary pregnane-3-glucuronide, a progesterone metabolite (Croxatto 1984).

At 3 to 4 months postpartum in 9 infants and 9 to 12 months postpartum in 7 infants, the metabolite levels were 6.3 ng/mL and 15.7 ng/mL, respectively, values that did not differ significantly from those in infants whose mothers were using a CuT380A IUD. Based on the pregnane-3-glucuronide levels, it was estimated that infants ingesting 800 mL of breast milk daily were receiving approximately $5 \, \mu\text{g}$ of progesterone from breast milk. As the maximum intake of exogenous progesterone should not exceed $150 \, \mu\text{g}/\text{day}$ according to international guidelines, this indicates that the progesterone delivered from the ring and its fraction secreted in the mother’s milk, should be harmless to the baby (EMEA Committee for Veterinary Medicinal Products. Progesterone: Summary Report 1999).

Progesterone has a short half-life (3 to 90 minutes) and due to rapid absorption from the gastrointestinal tract and extensive hepatic metabolism, the bioavailability of orally administered exogenous P is less than 10% (Stanczyk 2002). It is unlikely that the low amount of P excreted in the milk can affect the infant, especially as progesterone taken orally is quickly destroyed, and in clinical studies comparing PCVR to IUDs, there was no difference reported in infant growth between the 2 groups. (See Table 3)

Table 3: Comparative studies of Copper-T intrauterine device (IUD) or progesterone contraceptive vaginal ring (PCVR) used during breastfeeding and results on infant growth.

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Number women</th>
<th>Duration of exposure</th>
<th>Infant weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivin, 1997</td>
<td>IUD 734</td>
<td>IUD-533 WY</td>
<td>No difference at any point on time</td>
</tr>
<tr>
<td></td>
<td>PCVR 802</td>
<td>PCVR-431 WY</td>
<td></td>
</tr>
<tr>
<td>Chen, 1998</td>
<td>IUD 97</td>
<td>IUD- 889 WM</td>
<td>No difference at any point on time</td>
</tr>
<tr>
<td></td>
<td>PCVR 100</td>
<td>PCVR-538 WM</td>
<td></td>
</tr>
<tr>
<td>Massai, 1999</td>
<td>IUD 262</td>
<td>IUD- 2183 WM</td>
<td>No difference at any point on time</td>
</tr>
<tr>
<td></td>
<td>PCVR 285</td>
<td>PCVR- 2320 WM</td>
<td></td>
</tr>
</tbody>
</table>

*Duration of method use is expressed in Women-Years (WY) or Women-Months (WM).*

Interim results from ongoing Phase III trial in India: Similar findings have been reported from the ongoing Phase III trial in India in conjunction with the Indian Council of Medical Research (ICMR) (Evaluation of a Progesterone vaginal ring as a new contraceptive option in India: A joint collaborative study of the India Council of Medical Research, India and Population Council) (initiated in 2008). This study is examining safety and efficacy of the Progesterone Contraceptive Vaginal Ring (PCVR) versus a Copper Intra Uterine Device (CuT-380A IUD) in breastfeeding women. Among non-serious AEs reported as probably or highly probably related, 26 AE were in the PCVR group (total N enrolled = 459) and 19 in the IUD group (total N enrolled = 330). Most of the reports were related to bleeding problems: Menorrhagia (6 with PCVR and 10 with IUD), as well as prolonged spotting or bleeding (1 in each group). While CuT-380A IUD users reported post-coital contact bleeding (2), irregular spotting (1) and dysmenorrhea (1); PCVR users reported dyspareunia (1), white vaginal discharge (7), and irregular
bleeding (2). Also four cases of vaginal ulcers were reported, discovered at examination while the woman reported bleeding or dyspareunia and all case resolved after local treatment.

Discontinuation for increase vaginal discharge was seen in very few cases (mean 1.0±0.6 in PCVR at 270 days and 360 days of the study) and PID were reported as reasons for discontinuations in 0.2±0.2 in PCVR users at different time points of the study and 0.3 ±0.3 in the CuT380A IUD users at 180, 270 and 360 days of the study.

Interim safety results from the trial in India with about half of the total anticipated sample as of October 2014 are presented below.

Table 4a: Non-serious Adverse Events with probable and highly probably relationship to study product

<table>
<thead>
<tr>
<th></th>
<th>PVR (n=459)</th>
<th></th>
<th>IUD (n=330)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Disease of GenitoUrinary System</td>
<td>1</td>
<td>0.22</td>
<td>Bleeding P/V Post Insertion</td>
<td>1</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>1</td>
<td>0.22</td>
<td>Dysmenorrhea</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0.22</td>
<td>Irregular spotting and bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>6</td>
<td>1.30</td>
<td>Mechanical complication of IUD</td>
<td>1</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>2</td>
<td>0.43</td>
<td>Menorrhagia</td>
<td>10</td>
</tr>
<tr>
<td>PID</td>
<td>3</td>
<td>0.65</td>
<td>Metrorrhagia</td>
<td>2</td>
</tr>
<tr>
<td>Prolong Spotting</td>
<td>1</td>
<td>0.22</td>
<td>Postcoital and contact bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Ulceration of vagina</td>
<td>4</td>
<td>0.87</td>
<td>Prolonged spotting</td>
<td>1</td>
</tr>
<tr>
<td>White Discharge PV</td>
<td>7</td>
<td>1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular bleeding/spotting</td>
<td>1</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfunctional bleeding</td>
<td>1</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>6.09</td>
<td>Total</td>
<td>18</td>
</tr>
</tbody>
</table>

Interim report of the Indian study; reported at the ICCR meeting October 2014.

There were 13 morbidities reported in infants of PCVR users and 14 in CuT380A IUD users. These included childhood illnesses not uncommon in India such as measles, chicken pox and upper respiratory infections. There was no relationship in any reported case to the mother’s treatment.
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

Range of costs of the proposed medicine: For the public sector, the proposed suggested cost for the PCVR is USD $15 for 3 months or USD $5 per month. At current capacity the finished product manufacturing cost is USD $6.90. Cost of goods sold (COGS) and landed costs combined to achieve an average of USD $7.90. The addition of administrative and communications costs, result in a total USD $15 proposed cost to the public sector. Currently, the private sector costs range from USD $18-$36 in Latin America based on email correspondence from the manufacturer Grünenthal. The public sector price for developing countries, however, will depend on the volume of procurement and financing strategies for reducing the price to consumers in the poorest countries. A willingness to pay and procure study on the PCVR is currently underway in the public and private sectors in Kenya, Nigeria and Senegal.

Comparative cost-effectiveness presented as range of cost: The Progering® has no similar comparator. Although there are other methods of contraception available during lactation, none use the vaginal route for administration. Clinical methods such as implants, injectables, and IUDs rely on the availability of specialized equipment and supplies, protocols for infection prevention, and require a trained provider. Most importantly, they are not woman-controlled—users cannot choose to insert or remove the product without assistance from a trained medical provider. Although there have been strides towards bringing these methods closer to users by making them available at community-level health facilities and through frontline family planning providers through task-sharing arrangements, the process has been arduous and the uptake gradual. POPs and barrier methods are relatively easier to provide, but require daily, consistent action for effective use. Furthermore, supply shortages and stock outs mean that users that rely on methods that require frequent purchases may be unable to purchase contraception. In addition POP contain synthetic progestins that carry other effects than progesterone itself.

The Council has negotiated a cost-plus price agreement with the PCVR manufacturer for public sector rings. This agreement ensures that public sector rings will be available at the lowest possible cost. At the current negotiated public sector price of USD $15 for 3 months, the cost per month would be USD $5. Currently about 2000 vaginal rings are available annually at no cost for research purposes in developing countries.

Based on information from Grünenthal, the comparative prices in Chile for contraceptives that can be used during lactation are the following: Etonogestrel implant USD $60 for 3 years (about USD $5/month) plus the costs of trained provider; MPA injectable $8 for 3 months; progestin only pills (blister of 28 tablets) USD $0.4, as compared to Progering® at USD $5 /month (USD $15 for a 3-month ring). As with all contraceptive products, prices vary by country, market segment and the degree of financing for subsidized pricing by the government. Most contraceptive products currently on the public market in developing countries receive preferential prices or subsidies during procurement by donors and the government. Table 5 provides the comparative costs of other products provided by the public sector in developing countries during the first year of use (Singh & Darroch, 2012).
**Table 5: Comparative Cost of Contraceptive Products in Developing Country Markets**

<table>
<thead>
<tr>
<th></th>
<th>Female Sterilization</th>
<th>IUD</th>
<th>Implant</th>
<th>Injectable</th>
<th>Pill</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yearly Direct Costs</strong></td>
<td>$2.79</td>
<td>$1.01</td>
<td>$7.74</td>
<td>$9.14</td>
<td>$8.72</td>
</tr>
<tr>
<td><strong>Approximate Year 1 Direct Costs</strong></td>
<td>$30.69</td>
<td>$3.99</td>
<td>$24.51</td>
<td>$9.14</td>
<td>$8.72</td>
</tr>
</tbody>
</table>

**REGULATORY INFORMATION**

13. **Summary of regulatory status of the medicine (in various countries)**

The product is registered under the brand name Progering® in 8 countries in Latin America: Bolivia, Chile, Dominican Republic, Ecuador, El Salvador, Guatemala, Panama, and Peru. Submissions for regulatory approval in Columbia, Honduras and Paraguay are either complete or nearly complete. Submissions for regulatory approval are currently being prepared for Brazil and Mexico. The PCVR has not been developed or registered in the USA or in Europe, given the low levels of exclusive breastfeeding in those markets.

A large Phase III study is ongoing in India with the Indian Council of Medical Research for the purpose of obtaining registration with the Drug Controller of India.


Progesterone is a known compound in the international pharmacopoeia. The formulation discussed in this application is natural progesterone as opposed to the synthetic progestins available on the market.

15. **Proposed new text that could be included in a revised WHO Model Formulary**

**Indication:** Progesterone Vaginal Ring for Contraception (PCVR) during breastfeeding.

The PCVR delivers a dose of progesterone at 10mg/day for 3 months, through continuous use of the vaginal ring. This method is indicated from 4 weeks postpartum up to one year, in women who are actively breastfeeding at least 4 times a day.

**Contraindications:** Progesterone is a natural hormone for which contraindications are not known in the doses delivered by the ring. Nevertheless, hypersensitivity to any of the components of the vehicle, although no cases exist, is considered a contraindication as well the presence of a genital tract infection (e.g. endometritis in the postpartum). In the case of infection, the ring should not be used until the infection has been controlled (Progering® Monograph 2004).

**Precautions:** In case of dyspareunia, genital actinomycosis, suspected or actual endometrial or cervical neoplastic pathology, recurrent urinary and vaginal infections, the specialist must evaluate if the use of the ring represents an additional risk for each patient. If vaginal infections occur during use, they must be treated and the healthcare professional must decide if the ring should be removed. In this case,
the treatment with a new ring can be reinitiated once the infection is under control. It is recommended
to instruct the woman who uses the ring to consult a treating provider in cases of pain, secretion with
bad odor and/or genital injuries (Progering® Monograph 2004).

Dosage, Mode of Administration: One vaginal ring is recommended for use for 90 days with an
additional 10 day allowance from 4 weeks up to one year postpartum among women who breastfeeding
at least 4 times a day. The ring releases progesterone at an average daily rate of 10 mg during 3
months of continuous use; four rings may be used successively up to 1 year.

Adverse Events (AEs): The AEs occurring in previous studies with PCVRs have generally been non-
serious, mild and typical of those reported by women using progestin-only contraceptives. AEs that
have occurred are easily controlled and most occur in less than 1% of users. In the largest
comparative study conducted to date, vaginal problems, the most frequently occurring AE, were
reported by a higher percentage of women using the PCVR than the CuT380A IUD (25.8% vs 16.8%; P
<0.001); however, fewer women using the PCVR than the CuT380A IUD experienced abnormal findings
on the vaginal examination (14.8% vs 19.9%, P < 0.01). Abnormal findings on vaginal examination
included discharge, vaginitis, mycosis (yeast), trichomonas, other organisms, and “other.” Vaginal
discharge was observed more frequently among IUD users in a preregistration study of the PCVR in
Chile, vaginal problems were more frequently reported by users of the PCVR than the CuT380A IUD
(3.5 vs 1.9 per 100 woman-months; P = 0.005), but menstrual events were reported less frequently by
PCVR users (0.6 vs 1.4 per 100 woman-months; P=0.008) as was low abdominal pain (1.8 vs 3.0 per
100 woman-months; P= 0.009).

No serious adverse events have been reported in women who used similar progesterone contraceptive
vaginal rings in previous clinical trials, in a clinical trial ongoing in India in conjunction with the Indian
Council of Medical Research (ICMR) or in post marketing surveillance conducted by the manufacturer.
References


Appendices (see attached PDF files)

- Appendix I: WHO RHR GRADE Table for progesterone-releasing vaginal rings in breastfeeding women

- Appendix II: Key documents