ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dapivirine Vaginal Ring 25 mg vaginal delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Dapivirine Vaginal Ring contains 25 mg of dapivirine and releases approximately 4 mg of dapivirine over a period of one month.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal delivery system.

The Dapivirine Vaginal Ring is a flexible, off-white vaginal ring with an outer diameter of 56 mm and a cross-sectional diameter of 7.7 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 18 years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available.

4.2. Posology and method of administration

Posology

One Dapivirine Vaginal Ring is inserted into the vagina and kept in until replaced each month with a new ring. To maintain efficacy, a new Dapivirine Vaginal Ring should be inserted immediately after the previous ring is removed.

The Dapivirine Vaginal Ring must be used as directed (see "Method of administration"). If the Dapivirine Vaginal Ring is accidentally expelled or removed, the woman should follow the instructions given below under "Accidental expulsion or removal".

Special populations

Paediatric population
The safety and efficacy of the Dapivirine Vaginal Ring in children under the age of 18 years have not been established.

Currently available data are described in section 4.8 but no recommendation on a posology can be made.

Method of administration

Vaginal use

Preparation for inserting the Dapivirine Vaginal Ring
The woman should wash her hands in clean water and dry them before removing the Dapivirine Vaginal Ring from the package.

The woman should choose a position that is comfortable for her to insert the Dapivirine Vaginal Ring, for example raising one leg, squatting or lying down (Figure 1A–C).

Figure 1: Positioning for Inserting the Dapivirine Vaginal Ring

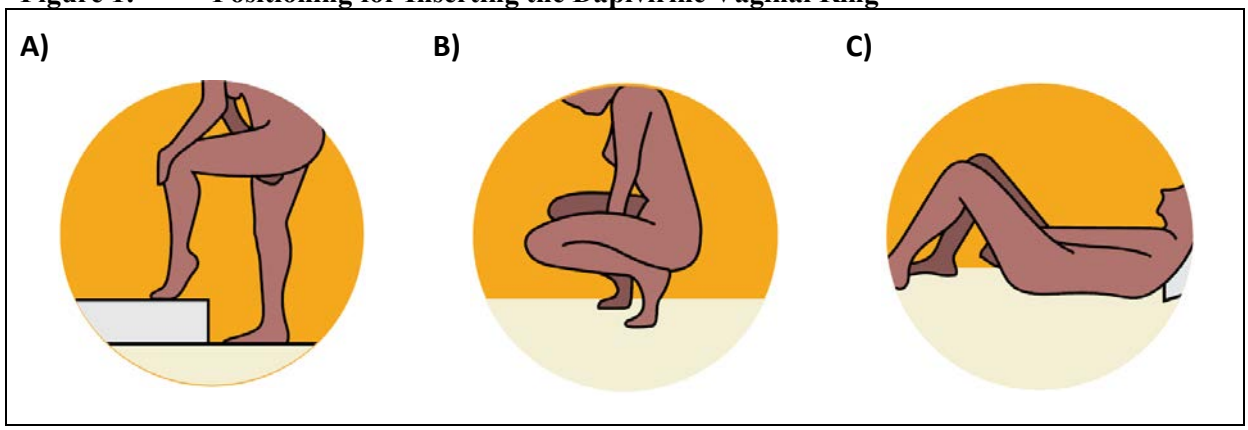
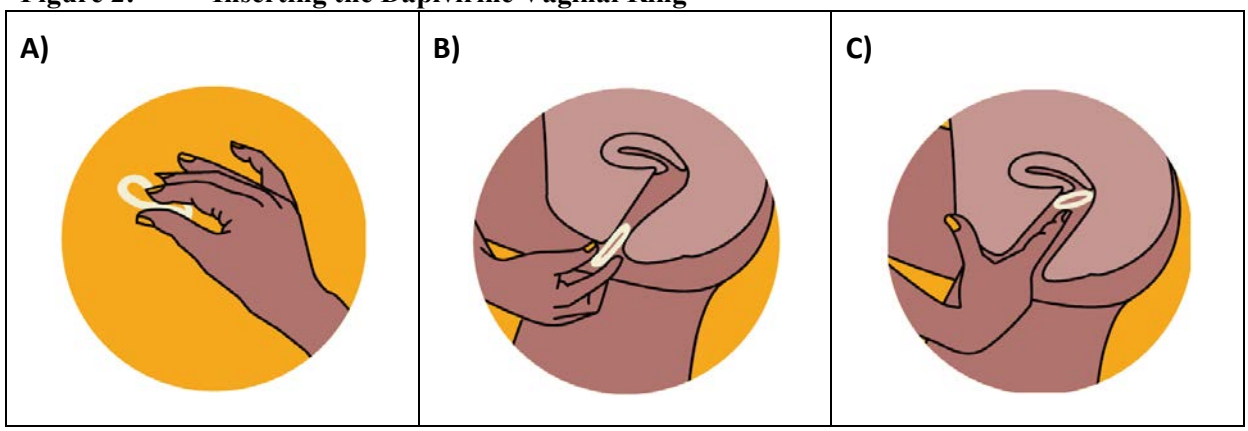
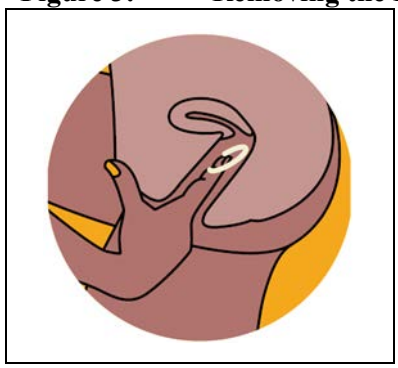


Figure 2: Inserting the Dapivirine Vaginal Ring



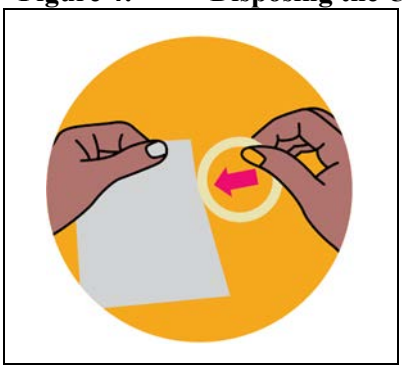
The Dapivirine Vaginal Ring should be held between the thumb and index finger, twisting it into the shape of the number eight (8) or pressing the sides together (Figure 2A). Using the other hand, the folds of the skin around the vagina should be held open. The tip of the ring should be placed in the vagina opening (Figure 2B), and then the index finger should be used to gently push the folded ring into the vagina as far as possible (Figure 2C). If the ring feels uncomfortable, it may not have been pushed far enough into the vagina. In this case, the woman should use her index finger to gently push the ring as far as she can. If the ring still feels uncomfortable, the woman should try re-inserting the ring or contacting her healthcare provider. Once the ring is inserted, the woman should wash her hands in clean water and dry them.

Figure 3: Removing the Dapivirine Vaginal Ring



The woman should wash her hands in clean water and dry them, choose a comfortable position with her legs apart, and use her finger to hook the ring and gently pull it out of her vagina (Figure 3).

Figure 4: Disposing the Used Dapivirine Vaginal Ring



To dispose the used Dapivirine Vaginal Ring, the used ring may be placed inside an empty pouch (Figure 4). Alternatively, the used ring may be wrapped in tissue or toilet paper. A refuse bin, which is kept out of reach of children, should be used for disposal. The ring should not be disposed in the toilet (see section 6.6). The woman should wash her hands in clean water and dry them after handling the ring.

Accidental expulsion or removal of the Dapivirine Vaginal Ring
The Dapivirine Vaginal Ring may be accidentally expelled (e.g. during a bowel movement, urination, menses or vaginal intercourse) or removed (e.g. when removing a tampon).

If accidental expulsion/removal occurs in a clean environment (e.g. whilst in bed or inside clean clothing), and the Dapivirine Vaginal Ring does not touch an unhygienic surface (e.g. the toilet), the woman may rinse the ring in clean water and immediately re-insert it, as instructed.

If the Dapivirine Vaginal Ring touches something unhygienic when accidentally expelled or removed, it should not be re-inserted and should be discarded as instructed (Figure 4). A new ring should be inserted immediately, following the instructions for inserting the Dapivirine Vaginal Ring (Figure 2).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use in women with unknown or positive HIV status.

4.4. Special warnings and precautions for use

Overall HIV-1 infection prevention strategy

The Dapivirine Vaginal Ring is not always effective in preventing HIV-1 infection. The time to onset of risk reduction after initial insertion or following reinsertion after the ring has been expelled or removed and not immediately replaced, is unknown.

The healthcare professional should perform a risk assessment to identify the most suitable prevention option(s) tailored to the woman's individual situation. The Dapivirine Vaginal Ring should only be used as part of an overall HIV-1 infection prevention strategy, including the use of other HIV-1 prevention measures, which could include consistent and correct condom use and regular testing for other sexually transmitted infections.

The Dapivirine Vaginal Ring is used locally in the vagina and only reduces the risk of HIV-1 infection in women by vaginal intercourse. The Dapivirine Vaginal Ring should not be removed prior to, during or after vaginal sexual intercourse.

Risk of HIV resistance with undetected HIV-1 infection

The Dapivirine Vaginal Ring should only be used in women confirmed to be HIV-1 negative, as per applicable local HIV testing guidelines. Women should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every 3 months) while using the Dapivirine Vaginal Ring (see section 4.3).

Continued use of the Dapivirine Vaginal Ring in the presence of HIV-1 infection could lead to the selection of viral mutations associated with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. Therefore, if clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposure to HIV-1 is suspected, the use of the Dapivirine Vaginal Ring should be delayed for at least one month and HIV-negative status should be confirmed before initiating or continuing the use of the Dapivirine Vaginal Ring.

Importance of adherence to product use

Women using the Dapivirine Vaginal Ring should be counselled to strictly adhere to the recommended continuous use of the ring and to replace it after one month.

Study data suggest that HIV-1 risk reduction is correlated with adherence to product use. If women do not adhere to using the product, there is no reduction in HIV-1 infection risk. Dapivirine concentrations in vaginal fluid decline rapidly following removal of the ring.

Pelvic inflammatory disease and genital infections including non-sexually transmitted vulvovaginal infections

It is not known whether continued use of the Dapivirine Vaginal Ring in women with unrecognised lower genital tract infections could potentially result in an increased risk of developing pelvic inflammatory disease. Therefore early detection and appropriate treatment of genital infection (including STIs) in women using the Dapivirine Vaginal Ring is considered important, as well as consideration given to treatment of sexual partners.

Concomitant use of vaginally administered antimicrobial products to treat vulvovaginal infections that have not been studied in clinical trials of Dapivirine Vaginal Ring is not recommended (see section 4.5).

Vaginal practices

No data are available on the effect of vaginal practices, including dry sex practices, on the safety and efficacy of the Dapivirine Vaginal Ring. Therefore, concomitant use of such practices with the Dapivirine Vaginal Ring is not recommended.

4.5. Interaction with other medicinal products and other forms of interaction

Due to the low systemic exposure to dapivirine in women using the Dapivirine Vaginal Ring, which does not exceed 2 ng/mL (see section 5.2), the risk of systemic drug-drug interactions is considered low and drug-drug interaction studies were focused on medicinal products potentially co-administered locally in the vagina.

In vitro studies have indicated that the main metabolic pathways for dapivirine are oxidation and glucuronidation mediated by CYP450 and UGT enzymes, respectively). In vaginal tissue, CYP450, but not UGT enzyme activity was detected (see section 5.2).

Oral hormonal contraceptives

Due to the low systemic concentrations, dapivirine is not expected to affect the pharmacokinetics of oral hormonal contraceptives and therefore, it is expected that dapivirine will not interfere with the efficacy and safety of co-administered oral hormonal contraceptives.

Vaginal miconazole

Co-administration of a single vaginal dose of 1200 mg miconazole, administered as an oil-based formulation in a vaginal capsule, with the Dapivirine Vaginal Ring was evaluated in a single clinical trial.

During the first few days following co-administration, dapivirine vaginal fluid levels were approximately 2 to 3-fold lower than levels observed in the absence of miconazole. Plasma concentrations of dapivirine were increased 1.2-fold after the third day following co-administration.

Miconazole concentrations in vaginal fluids were approximately 6-fold higher and miconazole concentrations in plasma were 4-fold higher following co-administration. These increases are not expected to be clinically relevant, as the increased plasma concentrations of miconazole are still 4-fold lower than those observed after administration of a 60 mg miconazole nitrate oral gel formulation.

The concurrent use of the Dapivirine Vaginal Ring and miconazole was well-tolerated. However, methodological problems limit the reliability of the pharmacokinetic results for both drugs. Moreover the clinical relevance of the reduced vaginal dapivirine levels upon co-administration with vaginal miconazole is unclear. Therefore, women should be advised to use additional preventive measures against HIV, when co-treated with vaginal miconazole.

Vaginal clotrimazole

Co-administration of clotrimazole administered as a (water-based) vaginal cream (50 mg/day clotrimazole) for 7 days with the Dapivirine Vaginal Ring was evaluated in a single clinical trial.

Dapivirine exposure in vaginal fluid was 20% higher during co-administration with clotrimazole. Dapivirine plasma exposure was similar with or without co-administration of clotrimazole. After repeated application of clotrimazole cream for 7 days, systemic exposure of clotrimazole in the presence of dapivirine was approximately 33% higher, whereas vaginal fluid concentrations were similar to levels observed when clotrimazole was used alone. These increases are not expected to be clinically relevant.

The concurrent use of the Dapivirine Vaginal Ring and clotrimazole was well-tolerated. However, due to methodological problems limiting the reliability of the pharmacokinetic results for both drugs, concurrent use of these products should be undertaken with caution.

Other vaginal products

No data are available on the concomitant administration of other vaginally administered products, including metronidazole and clindamycin. No data are available on concomitant use of other vaginal rings, such as contraceptive vaginal rings or diaphragms. Concomitant use of the Dapivirine Vaginal Ring with such products is not recommended.

Other forms of interactions

Use with condoms

The Dapivirine Vaginal Ring can be used with condoms and both should be used during vaginal sexual intercourse.

Clinical data show that the use of the Dapivirine Vaginal Ring does not affect the failure rate of male condoms, including slippage or breakage, or have an effect on the safety, tolerability, acceptability and user experience of male condoms.

Clinical data show that the use of the Dapivirine Vaginal Ring does not affect the failure rate of female condoms, including slippage, breakage, misdirection or invagination, and has no effect on safety, tolerability and acceptability of female condoms.

Menses and tampon use

The Dapivirine Vaginal Ring should remain in the vagina during menses and can be used with tampons. Women should be careful not to accidentally remove the ring when removing a tampon. Dapivirine vaginal fluid concentrations decreased up to 4-fold during menses, but increased again thereafter and achieved concentrations consistent with the "no menses" group in a clinical trial by end of menses.

The use of tampons generally resulted in a further 2-fold decrease of dapivirine in vaginal fluid concentrations during menses. As the clinical relevance of the reduced vaginal dapivirine levels during menses and tampon use is unclear, women should be advised to use additional preventive measures against HIV during menses.

Ring removal during menses resulted in marked reductions in dapivirine concentrations in vaginal fluid, therefore continued use of the ring during menses is important.

Contact with vaginal fluids, and blood during menses, may change the colour of the ring during use. Such discolouration does not affect the mechanism of action in which Dapivirine Vaginal Ring protects against HIV-1 infection during vaginal sex.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of the Dapivirine Vaginal Ring in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity that are relevant to use of the Dapivirine Vaginal Ring (see section 5.3).

Although safety has not been established in pregnancy, the benefits of treatment should be considered for pregnant women at high risk of HIV infection, considering the subsequent risk of HIV transmission to the unborn child.

Breast-feeding

Dapivirine has been shown to be excreted in human milk. In one clinical study, dapivirine concentrations in breast milk from sixteen HIV-1 negative mothers who were lactating but not breast-feeding were 70% higher than in maternal plasma. However, since milk concentrations remained low (<1420 pg/ml), infant exposure to dapivirine is anticipated to be low (below 1 µg/day).

No formal studies have been conducted in women who are breast-feeding.

There is insufficient information on the effects of dapivirine in newborns/infants.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from use of the Dapivirine Vaginal Ring. The benefit of breast-feeding for the child and the benefit of reducing the risk of HIV-1 infection for the mother should be taken into account.

Fertility

There are no clinical data on the effect of the Dapivirine Vaginal Ring on fertility. There are no data from animal fertility studies with vaginal administration of dapivirine.

Oral studies in rats have shown effects on fertility but only at exposure levels well in excess of maximum exposure resulting from human vaginal administration, indicating that this is of little relevance to use of the Dapivirine Vaginal Ring (see section 5.3).

4.7. Effects on ability to drive and use machines

The Dapivirine Vaginal Ring has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (i.e. reported by ≥5% of participants in the Dapivirine Vaginal Ring group) were:

- Urinary tract infection (15.2%)
- Vaginal discharge (7.1%)
- Vulvovaginal pruritus (6.5%)
- Vulvovaginitis (6.4%)
- Pelvic pain (6.2%)

Tabulated summary of adverse reactions

The adverse drug reactions observed in the clinical trials with the Dapivirine Vaginal Ring, are listed below (Table 1) according to frequencies defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1000).

Table 1: Tabulated summary of adverse drug reactions associated with the Dapivirine Vaginal Ring, based on pooled Phase II/III clinical trials

System Organ Class	Very Common	Common	Uncommon	Rare
Infections and infestations	Urinary tract infection	Vulvovaginitis Cervicitis	Cystitis	
Gastrointestinal disorders		Abdominal pain lower		Abdominal discomfort
Renal and urinary disorders		Dysuria	Pollakiuria Bladder pain	Micturition urgency
Reproductive system and breast disorders		Vaginal discharge Vulvovaginal pruritus Pelvic pain	Vaginal odour Cervix erythema Vulvovaginal discomfort Vulvovaginal pain Cervical discharge Cervix ecchymosis Pelvic discomfort Vaginal erosion Cervix oedema Uterine cervical erosion Cervix petechiae	Genital itching Genital discomfort Vulval abrasion
General disorders and administration site conditions			Suprapubic pain Application site discomfort	Application site pain
Injury, poisoning and procedural complications			Vaginal laceration	

Other special populations

Post-menopausal women
The safety of the Dapivirine Vaginal Ring over a 12-week use period has been evaluated in one placebo-controlled trial in post-menopausal women (n=96; 45-65 years of age). In this trial the most commonly observed adverse drug reactions (ADRs) (assessed as product-related by the Investigator) that were reported in more than 2 participants in either treatment group were vaginal discharge, lower abdominal pain, urinary tract infection, vulvovaginitis, vaginal odor, vulvovaginal erythema and vulvovaginal pruritus. These ADRs are consistent with ADRs reported in trials of women of reproductive age. Additional ADRs included cervix ecchymosis, cervical petechiae, vaginal ecchymosis and vaginal spotting. These events are not unanticipated for the enrolled population.

Paediatric population
The safety of the Dapivirine Vaginal Ring in adolescents aged 15-17 years was evaluated in a placebo-controlled trial. In total, 96 participants were enrolled and randomised: 73 participants to the Dapivirine Vaginal Ring group and 23 participants to the placebo ring group. The Dapivirine Vaginal Ring was well tolerated in adolescent females when inserted once every 4 weeks and used continuously during 24 weeks. The type and nature of adverse events reported were similar to those reported in trials conducted in women of reproductive age 18 years and older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9. Overdose

The potential for overdose using the Dapivirine Vaginal Ring is considered highly unlikely. No case of overdose has been reported in clinical trials. If an overdose occurs, standard supportive treatment should be applied as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gyneacological anti-infectives and antiseptics, ATC code: G01AX17

Mechanism of action

Dapivirine is an NNRTI with potent antiviral activity against HIV-1. It prevents viral replication by binding directly to HIV-1 reverse transcriptase (RT) and blocking its activity. Dapivirine binding is non-competitive against both the RNA template and the nucleotide substrate.

Pharmacodynamic effects

Antiviral activity
In vitro studies have shown that dapivirine inhibits HIV-1 replication with EC_{50} values ranging from 0.9 nM (0.3 ng/mL) to 12 nM (3.9 ng/mL) for laboratory isolates and from <0.5 nM (0.2 ng/mL) to 2.6 nM (0.9 ng/mL) in clinical isolates from HIV-1 subtypes CRF02_AG, B, C, D, CRF05_DF, H, CRF01_AE, and G.

Dapivirine has been shown to prevent HIV-1 infection of susceptible cells when present during viral exposure using monocyte-derived dendritic cells and autologous $CD4^+$ T-cells. In human ectocervical tissue explants >99% inhibition of HIV-1_{BaL} infection was observed at concentrations ≥10 nM (3.3 ng/mL), and transfer of free virus by migratory dendritic cells to indicator T-cells was blocked at

100 nM (32.9 ng/mL). Pre-treatment with 10 μM (3.3 μg/mL) dapivirine for 2 or 24 hours inhibited HIV-1 infection and virus dissemination by migratory cells for up to 6 days.

The activity of dapivirine is not significantly changed in the presence of semen and cervical mucus.

In vivo studies have shown that dapivirine inhibits infection in humanised severe combined immunodeficient (hu-SCID) mouse model when mice were challenged vaginally with HIV-1.

HIV resistance
In vitro susceptibility tests on HIV-1 isolates encoding one or more known NNRTI resistance mutations showed EC_{50} values of less than 100 nM (33 ng/mL) for 80% of tested isolates.

Selection of dapivirine-resistant strains occurs in vitro, with some strains requiring more than one substitution in the reverse transcriptase gene. The most frequently observed mutation during in vitro passage experiments is Y181C.

In analyses of dapivirine susceptibility, the following mutations showed a fold-change in susceptibility of >2 - ≤10: A98G, L100V, K101E, K103S, V106A, E138A/K/Q, Y181L; a > 10 - ≤ 100 fold-change was observed for: L100I, K103N, Y181C, G190Q, F227C and M230I/L; a > 100 fold-change was observed for: K101P, E138R, Y181I/V, Y188L and G190E. Multiple NNRTI mutations yielded increased susceptibility reduction with a >100 fold-change observed for double mutants: L100I+K103N, K103N+Y181C, V106A+F227C, E138A+F227C and Y181C+F227C.

Mutations observed in Phase III trials IPM 027 and MTN-020 included A98G, K101E, K103N, E138A, G190G/A, H221Y, K101E+E138A, K101E+E138G, K103S+V106M, V108V/I+E138A, E138A+V179D, E138A+V179I/T, K103K/N+V106V/M. An analysis of dapivirine susceptibility in viruses without genotypic mixtures showed 0.5 -19.3 fold-change (geometric mean: IPM 027: 3.06; MTN-020: 3.29).

The Phase III trials were performed in sub-Saharan Africa, where subtype C virus is the most common subtype. In these trials, a low and similar proportion of women in both Dapivirine Vaginal Ring and placebo ring groups had NNRTI mutations identified in samples taken soon after HIV-1 infection (IPM 027: Dapivirine Vaginal Ring: 16/84, 19.0%; placebo ring: 8/58, 13.8%; MTN-020: Dapivirine Vaginal Ring: 8/68, 11.8%; placebo ring: 9/96, 9.4%).

The most prevalent mutation observed in these trials was the E138A variant, with a higher proportion of participants who had virus with this variant noted in the Dapivirine Vaginal Ring group in one Phase III trial (IPM 027 trial) (11.9% [10/84]) compared to the placebo group (3.4% [2/58]; P=0.12, Fishers Exact Test), while no difference between treatment groups was observed in the other Phase III trial (MTN-020, 4.4% [3/68] vs 5.2% [5/96]). The E138A variant is a known polymorphism reported to have been observed in up to 8% of antiretroviral-naïve subtype C HIV-1 infected patients. The most frequently observed mutation during in vitro passage experiment, Y181C, was not observed in any Dapivirine Vaginal Ring-exposed participants in either of the Phase III clinical trials. Five participants in the Dapivirine Vaginal Ring group in IPM 027 had HIV-1 infection prior to enrollment. Four participants had genotypic testing at enrollment, seroconversion and Exit visits. Virus from one participant had E138A throughout. None had a change of genotype at seroconversion or the Exit visit.

In the IPM 027 trial the proportion of participants with more than one NNRTI resistance-associated mutation was comparable between the Dapivirine Vaginal Ring group and the placebo ring group. There were more participants with more than one NNRTI resistance-associated mutation in the Dapivirine Vaginal Ring group in the MTN-020 trial (7.3% [5/68] of participants in the Dapivirine Vaginal Ring group and 1% [1/96] of participants in the placebo ring group). In virus of three of the five participants, one of the mutations was the E138A polymorphism.

The mechanism by which differences between treatment groups arose is not clear (i.e. whether through passive transmission of resistant variants or active selection pressure through use of the Dapivirine Vaginal Ring).

In general, genotypic analyses indicated that high level resistance to the NNRTIs efavirenz and nevirapine, commonly used in the treatment of HIV/AIDS, was infrequent in both treatment groups. Phenotypic analysis of virus with the E138A substitution indicated that full susceptibility or only small reductions in susceptibility to other NNRTIs occurred in these viruses from both the Dapivirine Vaginal Ring and placebo ring groups.

Exposure to dapivirine following HIV-1 infection was limited and no conclusions can be drawn regarding the risk of resistance emerging with longer-term exposure to the Dapivirine Vaginal Ring in an HIV-1 infected woman.

NNRTI resistance associated mutations observed in the open-label extension trials (IPM 032 and MTN-025) were consistent with those observed in the Phase III trials. These mutations included A98G, K101E, K103N, E138A, E138A with V179D and V106M with V179D. A higher proportion of NNRTI mutations was observed in the open label trials (IPM 032: 5/17, 29.4% and MTN-025: 6/33, 18.2%) compared to the pivotal trial IPM 027 (16/84; 19.0%).

Clinical efficacy

The efficacy of the Dapivirine Vaginal Ring was assessed in the IPM 027 trial, a randomised, double-blind, placebo-controlled Phase III trial conducted in sub-Saharan Africa. The participants (healthy, sexually active women; 18 to 45 years of age) were instructed to use the Dapivirine Vaginal Ring continuously following insertion, and replace it with a new Dapivirine Vaginal Ring once every 28 days for a planned duration of 24 months.

The primary endpoint was the rate of HIV-1 seroconversion, and efficacy of the Dapivirine Vaginal Ring was assessed by comparing the risk of HIV-1 infection between the Dapivirine Vaginal Ring and the placebo ring groups. The primary efficacy analysis, based on data as of a cut-off date of 16 October 2015, showed that Dapivirine Vaginal Ring reduced the risk of HIV-1 infection by 35.07% (unadjusted 95% CI: 9.05 to 53.64) relative to placebo (Table 2).

Table 2: Summary of efficacy of the Dapivirine Vaginal Ring in Phase III clinical trial IPM 027: Primary analysis (Cut-off date 16 October 2015) – Modified intent-to-treat population

	Dapivirine Vaginal Ring	**Placebo Ring**	**Dapivirine Vaginal Ring vs Placebo Ring**
Number of participants in m-ITT population[a]	1302	650	
Number of confirmed trial endpoints[b]	80 (6.1%)	59 (9.1%)	
Number of censored values[b, c]	1222 (93.9%)	591 (90.9%)	
Total person years of follow-up	1889	917	
HIV-1 seroconversion rate[d] (per 100 person years[e]) (95% CI)	4.23 (3.31; 5.16)	6.43 (4.79; 8.08)	0.65 (0.46; 0.91)
Percentage reduction in HIV-1 seroconversion (95% CI)			35.07 (9.05; 53.64)
Treatment effect – *P*-value[f]			0.0114

CI = confidence interval, HIV = human immunodeficiency virus, m-ITT = modified intent-to-treat population: includes all participants who were randomised and were HIV-negative at enrollment

[a] 2:1 randomisation.

[b] The number of participants in the m-ITT population is the denominator for the calculation of percentages.

[c] HIV-seronegative participants were censored at the date of the last negative HIV-1 rapid test result.

[d] Hazard ratio and the unadjusted 95% confidence interval for the hazard ratio were estimated based on a Cox proportional hazards model stratified for research centre.

[e] Person-years were based on the cumulative follow-up time (i.e. time to first positive HIV-1 rapid test date or time to censoring). Follow-time is based on the double-blind on-treatment period.

[f] Two-sided log-rank test, stratified by research centre.

Based on the time to first HIV-1 RNA detection, a risk reduction of 35.0% was observed (unadjusted 95% CI, 8.97 to 53.59; $P = 0.0115$ based on a two-sided Log-rank test). The first detection of HIV-1 RNA was further used as the endpoint in the time-varying analyses, which correlated adherence to correct use of the product based on dapivirine concentrations in plasma and residual levels in used rings with the time of HIV-1 infection. Results suggest that HIV-1 risk reduction is correlated with adherence to product use (where non-adherence was defined by >23.5 mg of residual dapivirine levels in a used ring or a plasma concentration of <95 pg/mL). The maximum level of HIV-1 infection risk reduction via vaginal exposure with consistent ring use could not be determined based on the available data; however, exclusion of participants who were clearly non-adherent resulted in a higher risk reduction (Table 3).

Table 3: HIV-1 infection rate adjusted for adherence to investigational product use in Phase III clinical trial IPM 027: Primary analysis (Cut-off date 16 October 2015) – Modified intent-to-treat population

	Adherent Dapivirine Vaginal Ring	**Non-Adherent Dapivirine Vaginal Ring**	**Placebo Ring**	**Adherent Dapivirine Vaginal Ring vs Placebo Ring**	**Non-Adherent Dapivirine Vaginal Ring vs Placebo Ring**
Number of confirmed trial endpoints	54	26	59		
Number of censored values[a]	897	308	591		
Total person years of follow-up[b]	1454	427	914		
Percentage reduction in HIV-1 seroconversion (95% CI)				38.12 (10.18 to 57.37)	26.73 (-18.19 to 54.58)
Adherence effect – *P*-value[c]				0.0116	0.2023

CI = confidence interval, HIV = human immunodeficiency virus, m-ITT = modified intent-to-treat
Non-adherence was defined by >23.5 mg of residual dapivirine levels in a used ring or a plasma concentration of <95 pg/mL.

[a] HIV-seronegative participants who did not HIV-1 seroconvert were censored at the date of the last negative HIV-1 rapid test result.

[b] Follow-up time over all participants during adherent and non-adherent time intervals, respectively. A participant can switch between the adherent and non-adherent risk set over time and thus contribute data to both adherence and non-adherence time. Follow-time is based on the double-blind on-treatment period.

[c] Cox proportional hazards model stratified for research centre and including adherence as a time-varying covariate. m-ITT: The m-ITT population consisted of all trial participants who were randomised and were HIV-negative at enrollment.

In women >21 years of age at baseline, the HIV-1 infection risk reduction was 38.61% (95% CI, 7.48 to 59.26). Lower risk reduction of 27.51% (95% CI, -31.30 to 59.98) was observed in the subgroup of women who were 18 to 21 years of age at baseline. There is no apparent biological rationale for this difference between age groups. Adherence to ring use (as measured by residual drug levels in used rings of ≤ 23.5 mg and plasma concentrations of ≥ 95 pg/mL) was lower in the younger age group. In the time-varying adherence analysis (based on time to first detectable HIV-1 RNA) in a modified intent-to-treat population, a risk reduction of 28.76% was observed in the participants who were 18 to 21 years of age at baseline and classified to be adherent. The risk reduction in participants who were > 21 years of age at baseline and classified to be adherent was 41.60% (Table 4).

Table 4: HIV-1 infection rate adjusted for adherence to investigational product use in Phase III clinical trial IPM 027: Primary analysis (Cut-off date 16 October 2015) – Modified intent-to-treat population

Age	**≤21 years**		**>21 years**	
Population	**Number of confirmed endpoints/total person-years of follow-up[a]**	**% Reduction in HIV-1 Infection Adherent versus Placebo (95%CI)[b]**	**Number of confirmed endpoints/total person-years of follow-up[a]**	**% Reduction in HIV-1 Infection Adherent versus Placebo (95%CI)[b]**
Trial IPM 027 m-ITT	46/645	28.76 (-37.11 to 62.99)	93/2150	41.60 (8.26 to 62.82)

Adherence was defined by ≤ 23.5 mg of residual dapivirine levels in a used ring and a plasma concentration of ≥ 95 pg/mL.
m-ITT: The m-ITT population consisted of all trial participants who were randomised and were HIV-negative at enrollment.

[a] Follow-up time over all participants during adherent and non-adherent time intervals respectively. A participant can switch between the adherent and non-adherent risk set over time and thus contribute data to both the adherence and non-adherence time. Follow-up time is based on the double-blind on-treatment period.

[b] *P*-value for Adherence effect (vs placebo) = 0.0196, based on Cox proportional hazards model stratified for research centre and including age at baseline as a covariate, adherence as a time-varying covariate and adherence*age at baseline as time-varying interaction.

Paediatric population

The safety and efficacy of the Dapivirine Vaginal Ring in women under the age of 18 years has not been established.

Conduct of trials in paediatric subjects (less than 18 years of age) is not a legal requirement in the EU for this type of application.

5.2. Pharmacokinetic properties

Absorption

Dapivirine is released from the ring in a sustained manner, distributed into vaginal fluid, and absorbed into surrounding tissues and plasma. Measurable dapivirine concentrations were detected in vaginal fluid and plasma within 1 to 4 hours after ring insertion (Figure 5A and 5B). Concentrations of dapivirine in vaginal fluid exceeding the in vitro HIV-1 IC_{99} by 1000-fold are achieved within 24 hours of ring insertion. At 4 to 24 hours after ring insertion, vaginal fluid concentrations (at all 3 sampling locations: cervix, ring area and introïtus) are similar to those on Day 28 after continuous ring use. Dapivirine plasma concentrations at 24 hours after ring insertion are also similar to those at 28 days after continuous ring use. Systemic concentrations of dapivirine observed in plasma with the use of the Dapivirine Vaginal Ring were low (< 2 ng/mL). Pharmacokinetic parameters in vaginal fluid (cervix) and plasma are summarised in Table 5.

Figure 5A: Mean (SD) dapivirine concentrations in vaginal fluid following continuous use of the Dapivirine Vaginal Ring for 28 days and after removal of the Ring on day 28 (IPM 028)

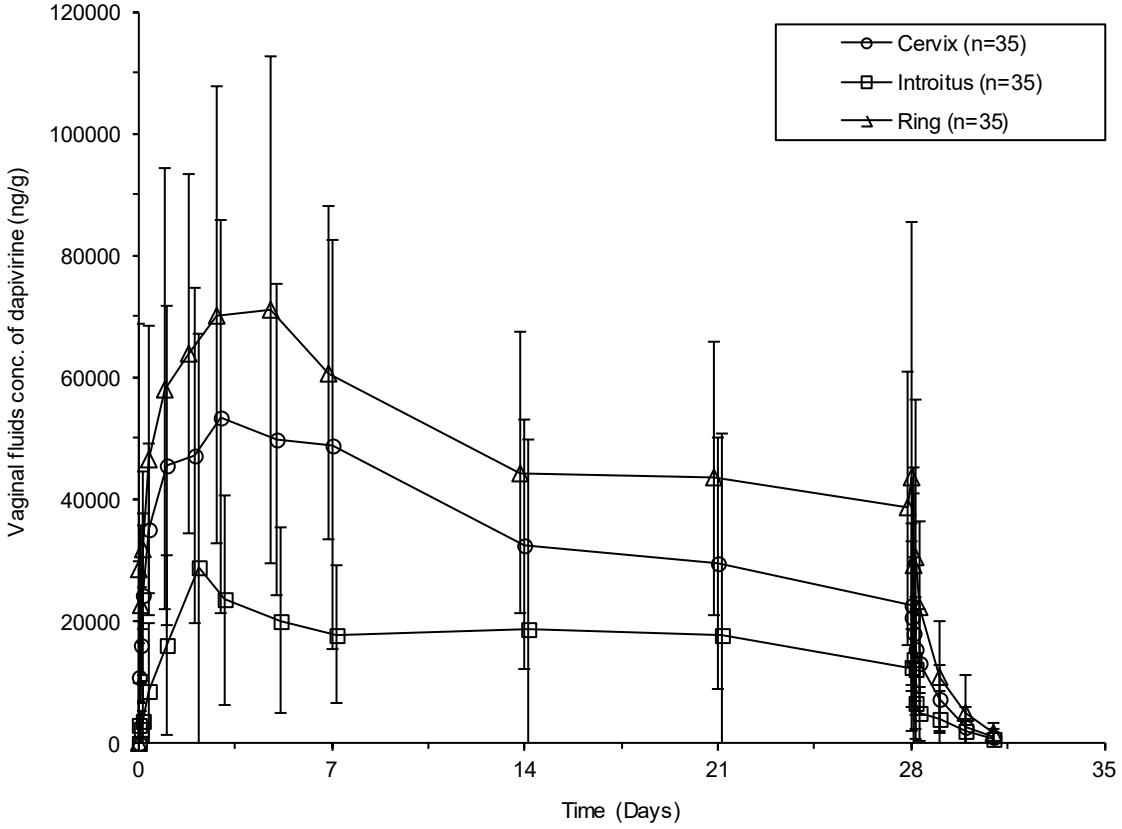


Figure 5B: Mean (SD) dapivirine concentrations in plasma following continuous use of the Dapivirine Vaginal Ring for 28 days and after removal of the Ring on day 28 (IPM 028)

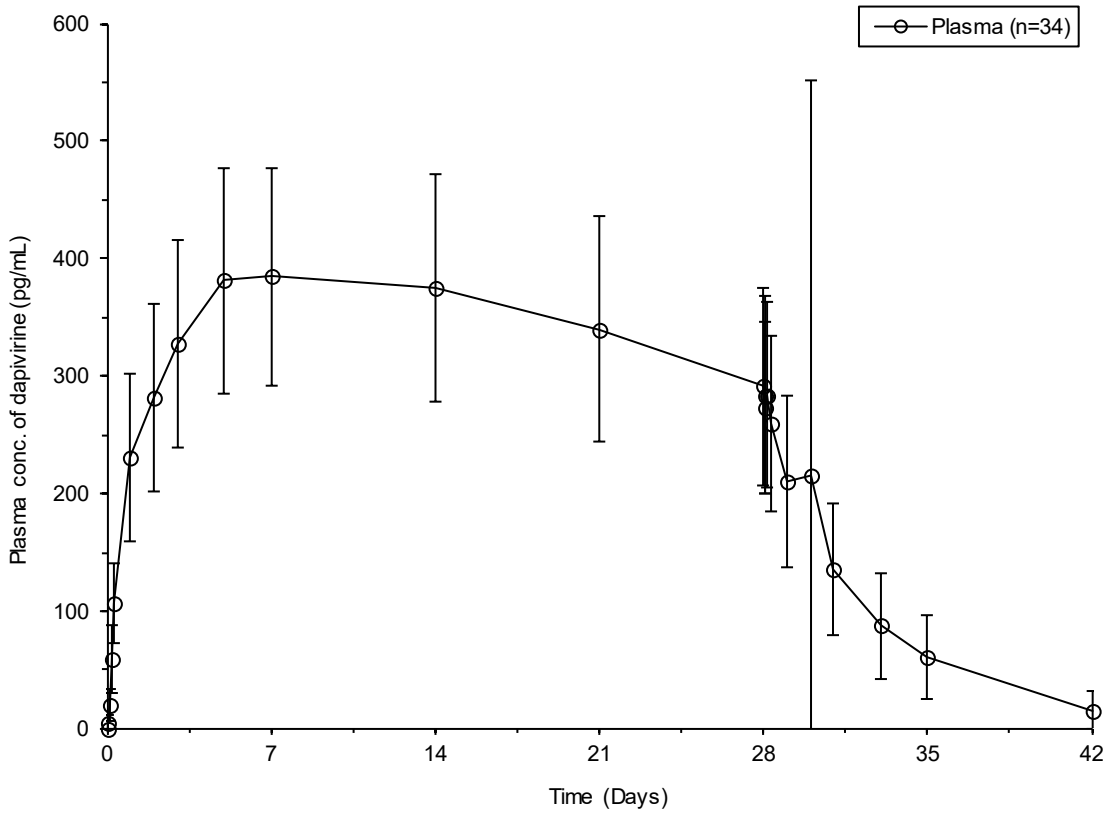


Table 5: Dapivirine pharmacokinetic parameters in vaginal fluid (cervix) and plasma during use of the Dapivirine Vaginal Ring for 28 days (IPM 028)

PK Parameter	Plasma	Vaginal fluid (cervix)
C_{max}	462.0 (288.0) pg/mL	76.9 (33.7) µg/g
T_{max}	167.90 (48.92 – 719.98) h	72.10 (8.07 – 336.23) h
$AUC_{0\text{-}28days}$	229408 (57399) pg.h/mL	24222 (10476) µg.h/g
C_{day28}	291.0 (83.4) pg/Ml	22.78 (13.16) µg/g
$t_{½,term}$	81.5 (21.8) h	13.1 (6.5) h

Values are mean (SD) for all parameters except T_{max} which is median (minimum, maximum).

Distribution

In cervicovaginal fluid, the in vitro protein binding of dapivirine is 15%. Dapivirine is highly bound to plasma proteins (> 99.6%) in vitro.

After vaginal administration of ^{14}C-dapivirine to non-pregnant rats, concentrations of drug-related material were highest in the vaginal wall, followed by small intestine wall, large intestine wall, stomach wall, liver, cecum wall, and abdominal fat. Concentrations in other tissues were very low.

In two clinical trials where cervical tissue biopsies were evaluated, the interindividual dapivirine concentrations in tissue after 28 days of using the Dapivirine Vaginal Ring were highly variable (ranging from 46-12900 ng/ml), with the lowest measured dapivirine concentration still 10 times the in vitro IC_{99} in cervical tissue.

The distribution of dapivirine into compartments other than plasma and vaginal fluid (e.g., cerebrospinal fluid) has not been evaluated in humans.

Biotransformation

In vitro experiments indicate that in the liver dapivirine primarily undergoes oxidative metabolism by cytochrome P450 (CYP450; primarily CYP3A and, to a lesser extent, by the CYP2C family), followed by glucuronidation by UGT1A and -2B isoenzymes.

In vitro studies in vaginal tissue suggest that CYP450-mediated metabolism also occurs in tissues at the site of application, but no evidence of glucuronidation was detected.

Limited data are available on the interaction of dapivirine with drug transporters, but dapivirine permeability was determined not to be P-gp dependent in vitro.

Dapivirine was not an inducer of CYP1A2, CYP3A4 or CYP3A5 in human hepatocytes at concentrations up to 100 ng/mL.

Elimination

In the overall clinical trial population, the terminal elimination half-life ($t_{1/2}$) of dapivirine was approximately 13 hours in vaginal fluid (cervix) and approximately 82 hours in plasma.

In clinical trials with orally administered dapivirine, dapivirine was shown to undergo negligible renal clearance.

Special populations

Renal and hepatic impairment
No clinical trials in women with renal or hepatic impairment have been performed. In view of the low systemic exposure of dapivirine, hepatic impairment is not expected to affect dapivirine exposure or

the safety profile. Similarly, based on low plasma concentrations and negligible renal clearance of dapivirine, renal impairment is not expected to affect dapivirine exposure or the safety profile.

Paediatric population
The pharmacokinetics of the Dapivirine Vaginal Ring have not been studied in children under the age of 15 years.

One clinical trial evaluated the mean dapivirine plasma concentration in adolescent girls aged 15-17 years. The mean dapivirine plasma concentrations in adolescents were comparable to the mean dapivirine plasma concentrations in adults.

Post-menopausal women
One clinical trial evaluated the mean dapivirine plasma concentration in post-menopausal women aged 45-65 years. The mean dapivirine plasma concentrations in these women were comparable to the mean dapivirine plasma concentrations in women of reproductive age.

Other special populations
Clinical data suggest that dapivirine vaginal fluid and plasma concentrations were within the same range in Black and Caucasian women.

Pharmacokinetic/pharmacodynamic relationship(s)

In the absence of a surrogate marker or model for risk reduction in HIV-1 infection acquired via vaginal intercourse, no in vitro-in vivo correlation studies or pharmacodynamic trials were performed.

Dapivirine activity in cervical tissue (99% inhibitory concentration [IC_{99}] in vitro against HIV-1_{BaL}=3.3 ng/mL) is considered relevant for the risk reduction of HIV-1 infection via the genital route. However, accurate determination of dapivirine concentrations within the target tissues is difficult because of the uncertainty of where measured drug concentrations are actually located (e.g., on the tissue surface, in the dead keratinized cell layers, or in interstitial fluid and living target cells). Therefore, dapivirine levels in vaginal fluid were used to provide information on the local distribution and exposure to dapivirine. Dapivirine vaginal fluid concentrations exceed the in vitro cervical tissue IC_{99} (HIV-1_{BAL}) by more than 1000-fold within hours after ring insertion and by more than 3000-fold within 24 hours after ring insertion, and these concentrations are maintained for at least 28 days during continuous ring use. After 28 days of ring use, dapivirine concentrations in vaginal fluid are still >3000-fold (at the introïtus) and >6000-fold (near the ring and the cervix) above the IC_{99}.

The ex vivo capacity of the vaginal fluid to protect susceptible cells from infection upon challenge in vitro with HIV-1 was tested using vaginal fluid samples collected by cervicovaginal lavage after ring removal. Despite the dilution due to the lavage fluid and likely loss of drug due to possible precipitation of dapivirine in the lavage fluid and adsorption of dapivirine to the collection equipment, the vaginal fluid samples contained sufficient dapivirine to inhibit in vitro HIV infection by a mean of 89%.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for women relevant to use of the Dapivirine Vaginal Ring based on conventional studies of safety pharmacology, repeated dose toxicity, irritancy, genotoxicity, carcinogenic potential and toxicity to reproduction and development. No clinically relevant local or systemic findings were seen in rabbits following vaginal administration of dapivirine for up to 9 months, at exposures well in excess of maximum human vaginal exposure.

Reproductive toxicity

There were no findings in embryo-foetal development studies in rats and rabbits following vaginal administration of dapivirine at systemic exposures in excess of those in women using the Dapivirine Vaginal Ring.

In oral embryo-foetal development studies, embryo-foetal toxicity (increased post-implantation loss, decreased foetal body weight, increased cardiac and skeletal malformations/anomalies, and reduction in skeletal ossification) was seen at maternally toxic doses in rats (more than 1000-fold higher than those resulting from maximum human vaginal exposure, based on C_{max} and AUC_{24h}), but not in rabbits.

In a rat oral pre-and post-natal development study, effects on offspring body weight were associated with maternal reductions in body weight gain and food consumption. No effects were seen at an exposure more than 1000-fold higher than that resulting from maximum human vaginal exposure (based on C_{max} and AUC_{24h}).

In a rat oral fertility study, increased post-implantation loss, decreased body weight and weight gain pre-mating and during the post-coitum period, and decreased fertility and conception were seen at high doses. No effects were seen at an exposure more than 1000-fold higher than that resulting from maximum human vaginal exposure (based on C_{max} and AUC_{24h}).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dimeticone, 1,000 centistokes (cSt)
Silicone Elastomer (DDU-4870):
- Siloxanes and Silicones, dimethyl, vinyl group-terminated
- Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane
- Silica, amorphous, fumed, crystalline free
- Siloxanes and silicones, dimethyl, methyl vinyl, methyl hydrogen, hydroxyl-terminated

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5. Nature and contents of container

Each Dapivirine Vaginal Ring is packaged into a laminated (PET-Alu/Adhesive/PP), square, heat-sealed pouch. Specific materials of construction:

- PET-Alu - 48 ga. Metallized Polyester (Polyethylene Terephthalate with aluminum)
- Adhesive - Mor-Free L75-164
- PP - 1.5 mil Polypropylene

Pack-sizes of either one pouch or three pouches.

6.6. Special precautions for disposal

The used Dapivirine Vaginal Ring should either be placed in an empty pouch or wrapped in tissue or toilet paper and disposed in the refuse bin, out of reach of children. The Dapivirine Vaginal Ring should not be disposed in the toilet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

International Partnership for Microbicides Belgium (IPM Belgium) AISBL
Square de Meeûs 38/40
1000 Brussels
Belgium

8. SCIENTIFIC OPINION NUMBER(S)

Not applicable

9. DATE OF FIRST SCIENTIFIC OPINION/RENEWAL OF THE SCIENTIFIC OPINION

Date of first Scientific Opinion: 23 July 2020

Date of latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

QPharma AB
Agneslundsvägen 27
212 15
Malmö
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- **Periodic safety update reports (PSURs)**

The scientific opinion holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every year until otherwise agreed by the CHMP.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of the Dapivirine Vaginal Ring the scientific opinion holder must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at the healthcare professional and the patient (user). The main objectives are to provide information for counselling which address the safety concerns and to minimise potential adverse outcomes in the user with emphasis on adherence and the importance of regular (3 monthly) confirmation of HIV-1 seronegative status during use of the Dapivirine Vaginal Ring. Additionally, the Patient (User) Guide will contain explanations on how to use the product correctly.

The scientific opinion holder shall ensure that in each country where the Dapivirine Vaginal Ring is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use the Dapivirine Vaginal Ring have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (HCP guide)

Guide for healthcare professionals:

Relevant information of the safety concern(s) addressed by the HCP guide include the following key messages:

- The importance of continuous use of the vaginal ring during one month and immediate replacement of the Dapivirine Vaginal Ring with a new ring after 1 month.
- The Dapivirine Vaginal Ring should be used in combination with safer sex practices and that it can only protect against HIV-1 infection from vaginal sex.
- Because limited information is known about the effect of vaginal practices such as douching and dry sex practices on dapivirine, it is recommended to avoid any vaginal practices which may potentially interfere with the Dapivirine Vaginal Ring.
- The importance of regular monitoring of HIV status to avoid starting or continuing to use the Dapivirine Vaginal Ring if HIV infected, and what signs and symptoms to look out for during HIV seroconversion (early stages of HIV infection).
- The Dapivirine Vaginal Ring does not prevent pregnancy and does not protect against transmission of other STIs.
- The importance of recognizing and receiving treatment early when STIs or other infections in the vagina occur, which might increase the risk of HIV infection.
- Provide advice on what actions to take in case the Dapivirine Vaginal Ring accidentally falls out of the vagina or is damaged.
- Information that it is not known if the Dapivirine Vaginal Ring is safe to use in women who are pregnant or breastfeeding.

The patient information pack:

- Patient information leaflet
- A patient (user) guide

Patient (user) guide:

Relevant information of the safety concern(s) addressed by the User guide include the following key messages:

- A description of what a normal Dapivirine Vaginal Ring looks like and what to do if the ring is damaged or broken or looks different to what is expected.
- An instruction that the Dapivirine Vaginal Ring should only be inserted into the vagina.
- The Dapivirine Vaginal Ring may only protect from HIV-1 during vaginal sex and does not protect from HIV-1 infection during anal sex or other forms of sexual contact as well as other ways of becoming infected with HIV (eg, sharing needles when using recreational drugs).
- The Dapivirine Vaginal Ring does not protect a man from getting HIV-1 infected.
- Safer sex practices (such as use of condoms) should always be used at the same time as using the Dapivirine Vaginal Ring and that male and female condoms can be safely used together with the Dapivirine Vaginal Ring.
- The Dapivirine Vaginal Ring should be kept in the vagina at all times, (even during menstruation and especially during vaginal sex), until it is replaced with a new one after 1 month.
- It is safe to use the Dapivirine Vaginal Ring with tampons during menstruation. If tampons are used and later removed, it should be ensured not to accidently remove the vaginal ring as well.

- If the Dapivirine Vaginal Ring accidently falls out or is removed and this happens in a clean place (eg, in the bed or in a cloth), the vaginal ring should immediately be rinsed in clean water and inserted again into the vagina. If the vaginal ring has touched something dirty (eg, toilet) the vaginal ring should not be re-used but rather a new vaginal ring has to be inserted.
- The Dapivirine Vaginal Ring does not prevent pregnancy.
- Instructions to inform the HCP about any vaginal products regularly used to clean the vagina.
- A recommendation not to use products to clean the vagina when using the Dapivirine Vaginal Ring.
- Provides guidance that the user should contact her clinic or doctor if

    - the user suspects she may be HIV-infected and what the signs and symptoms of early HIV infection are.
    - the Dapivirine Vaginal Ring causes persistent discomfort or pain which does not resolve after repositioning the ring.
    - the user experiences signs or symptoms suggestive of pelvic inflammatory disease or a genital infection
    - the user suspects she is pregnant and to remove the vaginal ring immediately

- **Obligation to conduct post-authorisation measures**

The scientific opinion holder shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): Phase IV, open label, multicentre efficacy study in healthy HIV-negative young women age 18-25 years (stratified for 18 to 21 years and >21 to 25 years) using the Dapivirine Vaginal Ring over a period of 12 months to address the current uncertainty in the efficacy in younger women and to confirm the overall effect size by establishing an appropriate counterfactual and to systematically collect information about NNRTI resistance in seroconverters. Minimum requirements should be as follows: 1. Primary objective: • HIV-1 infection rate per 100 woman-years of product use at the end of the DVR use period • Incidence of NNRTI resistance mutations in participants who become HIV-1 infected 2. Secondary objective: • Assessment of genitourinary safety of the DVR, when inserted at monthly intervals, over a period of 12 months 3. Enrolment is expected to be as a minimum of around 2,000 HIV-negative young women age 18-25 years	Final CSR Q3 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Dapivirine Vaginal Ring 25 mg vaginal delivery system
dapivirine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Dapivirine Vaginal Ring contains 25 mg of dapivirine and releases approximately 4 mg of dapivirine over a period of one month.

3. LIST OF EXCIPIENTS

Silicone elastomer and dimeticone

4. PHARMACEUTICAL FORM AND CONTENTS

1 Vaginal delivery system.
[3 Vaginal delivery systems].

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Vaginal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The used Dapivirine Vaginal Ring should be placed in an empty pouch, or wrapped in tissue or toilet paper and disposed in the refuse bin out of reach of children. The Dapivirine Vaginal Ring should not be disposed in the toilet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

International Partnership for Microbicides Belgium (IPM Belgium) AISBL
Square de Meeûs 38/40
1000 Brussels
Belgium

12. SCIENTIFIC OPINION NUMBER(S)

Not applicable

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted.>

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS POUCH

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dapivirine Vaginal Ring 25 mg, vaginal delivery system
Vaginal use

2. METHOD OF ADMINISTRATION

Vaginal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 Unit

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dapivirine Vaginal Ring 25 mg vaginal delivery system

dapivirine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your healthcare provider.
- This medicine has been prescribed for you only. Do not give it to others as it may harm them.
- If you get any side effects, talk to your healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dapivirine Vaginal Ring is and what it is used for

The Dapivirine Vaginal Ring is used to reduce the chance of women 18 years and older getting a HIV-1 infection during vaginal sex. It should always be used in combination with safer sex practices and should be used when oral PrEP is not/cannot be used or is not available.

The Dapivirine Vaginal Ring contains dapivirine, a medicine that can reduce the risk to become HIV-1 infected.

The medicine is released from the ring into the vagina slowly over one month.

The Dapivirine Vaginal Ring must be kept in the vagina all the time until it is replaced with a new ring after one month.

The Dapivirine Vaginal Ring is an off-white coloured ring that is easy to bend and should only be used in the vagina.

Ask your healthcare provider if you have any questions about how to prevent getting HIV infected or how to prevent spreading HIV to other people.

2. What you need to know before you use Dapivirine Vaginal Ring

Do not use Dapivirine Vaginal Ring:

- If you are infected with HIV-1 or you are unsure if you are infected with HIV-1. You must get tested to make sure that you do not already have HIV-1 infection. The Dapivirine Vaginal Ring can only help to reduce the chance of you getting HIV-1 **before** you are infected.

- **Some HIV tests may miss a recent infection in the early stages**. If you get a flu-like illness, it could mean you have recently been infected with HIV. The following may be signs of HIV infection:

  - tiredness
  - fever
  - joint or muscle pain
  - headache
  - vomiting or diarrhoea
  - rash
  - night sweats
  - enlarged glands in the neck or groin

- **Tell your healthcare provider about any flu-like illness** – either in the month before starting to use the Dapivirine Vaginal Ring, or at any time while using it.

- If you are allergic to dapivirine or any of the other ingredients of this product (listed in section 6).

Warnings and precautions

Talk to your healthcare provider before using the Dapivirine Vaginal Ring.

If you think you may have come into contact with HIV, tell your healthcare provider straight away. More tests may be needed to make sure you are still HIV negative.

It is important to use the Dapivirine Vaginal Ring all the time. Following the instructions on how to correctly use the Dapivirine Vaginal Ring will reduce your chance of becoming HIV-1 infected:

- Always keep the ring in the vagina, especially during vaginal sex and also while you are having your period. Replace the ring each month with a new ring.
- Use the ring all the time, not just when you think you might be at risk of HIV-1 infection.
- If you take the ring out, you are no longer protected from HIV-1 infection.

Overall HIV infection prevention strategy

- Just using the Dapivirine Vaginal Ring may not prevent you from becoming infected with HIV.
- Always practise safer sex to protect yourself from HIV infection.
- Use male or female condoms during sex to reduce contact with semen, vaginal fluids, or blood.
- Do not share personal items, such as razor blades, that can have blood on them.
- Do not share or re-use needles or other tools used for injecting drugs.
- Get tested for other sexually transmitted infections. These infections make it easier for HIV to infect you.

Ask your healthcare provider if you have any more questions about how to prevent getting HIV infected or spreading HIV to other people.

Risk associated with continued use of the ring, when infected

If you continue to use the ring while HIV-1 infected, the HIV-1 virus may undergo changes. These may lead to resistance of the virus and make it more difficult to treat with available anti-HIV treatments. It is important to get tested at least every 3 months for HIV infection.

No protection from HIV-1 infection other than through vaginal sex

The Dapivirine Vaginal Ring only protects against HIV-1 infection during vaginal sex. It does not protect against HIV-1 infection which can happen from any activity other than vaginal sex, such as anal sex, oral sex and exposure to blood or sharp objects that may have been in contact with infected blood.

Use during menstruation

Leave the Dapivirine Vaginal Ring in the vagina during your period.

Contact with vaginal fluids, and blood during your period, may change the colour of the ring during use. Such discolouration is not expected to affect the way the ring works.

Tampons can be used at the same time as the vaginal ring. If using tampons, be careful when removing the tampon, to prevent accidentally pulling out the ring.

Lower levels of the medicine (dapivirine) in the vagina were observed in some women during their period and with tampon use. It is unclear how this lower amount of medicine affects how well the ring works. As mentioned before, additional HIV prevention measures should always be used.

Vaginal practices

A healthy vagina cleans itself. Therefore, you should not use soap or other products to clean the inside of your vagina when using the Dapivirine Vaginal Ring.

You should not use any products to dry out your vagina for sex when using the Dapivirine Vaginal Ring.

These practices may affect how well the ring works to reduce your chance of getting HIV-1 infection.

Pelvic inflammatory disease and sexually transmitted or vaginal infections

The Dapivirine Vaginal Ring does not protect you against vaginal infections or sexually transmitted infections, other than HIV-1 infection. The presence of these commonly occuring infections in your vagina may lead to swelling and pain and cause damage to the lining of your vagina. You may then be at a higher risk of getting HIV infection.

These infections may also spread higher up in your vagina and cause a severe infection of your female organs higher up in your belly (pelvic region). It is important that you seek medical attention and treatment for these infections as soon as possible if you experience any symptoms such as itching, discomfort or pain in the vagina, a discharge from your vagina or severe pain in your lower belly.

Children and adolescents

The Dapivirine Vaginal Ring is not for use in women under 18 years of age.

Using Dapivirine Vaginal Ring when using other medicines

Tell your healthcare provider if you are taking, have recently taken or might take any other medicines or products that need to be put in your vagina.

Ask your healthcare provider before using any of these medicines or products while you are still using the Dapivirine Vaginal Ring.

Pregnancy and breast-feeding

The Dapivirine Vaginal Ring does not prevent pregnancy.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your healthcare provider for advice before using or continuing to use the Dapivirine Vaginal Ring.

Driving and using machines

You can drive or operate machinery as long as you feel well.

3. How to use the Dapivirine Vaginal Ring

Always use the ring exactly as your healthcare provider has told you. Check with your healthcare provider if you are not sure.

Use only one Dapivirine Vaginal Ring and insert it on the same date each month.

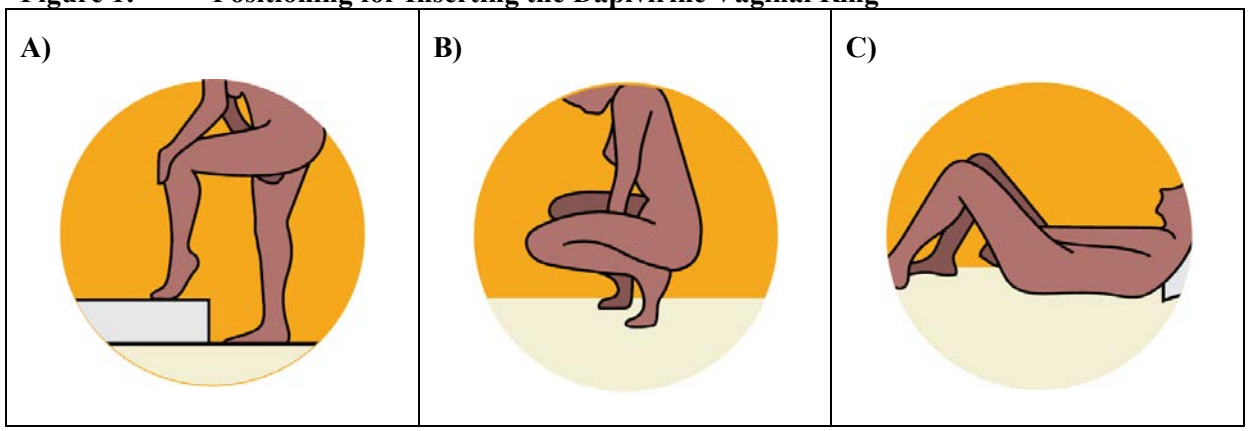
Follow the next steps for insertion of the Dapivirine Vaginal Ring:

Preparation

- Wash your hands in clean water and dry them.
- Remove the Dapivirine Vaginal Ring from the package.

Positioning

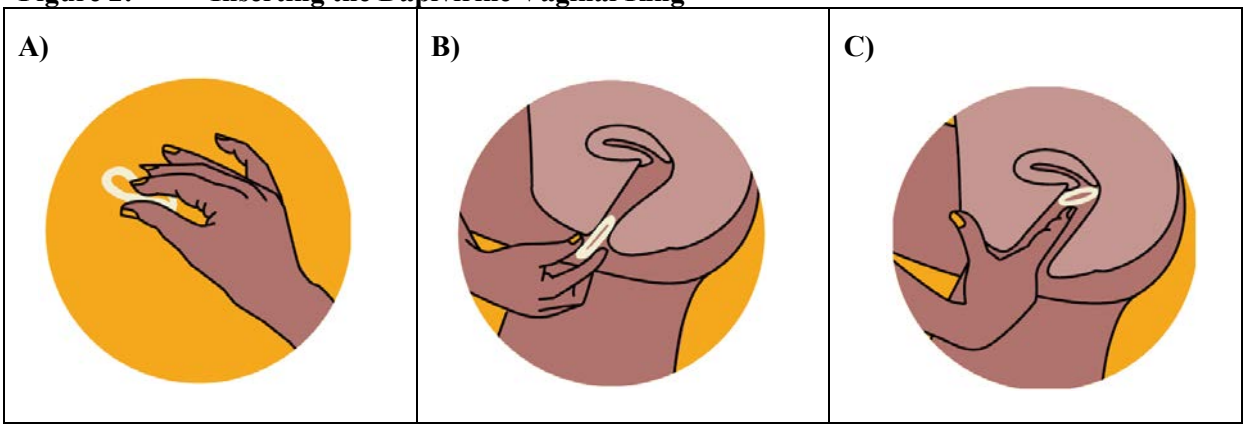
Figure 1: Positioning for Inserting the Dapivirine Vaginal Ring



- Find a comfortable position for insertion of the Dapivirine Vaginal Ring, this could be raising one leg, squatting or lying down (Figure 1A-C).

Insertion

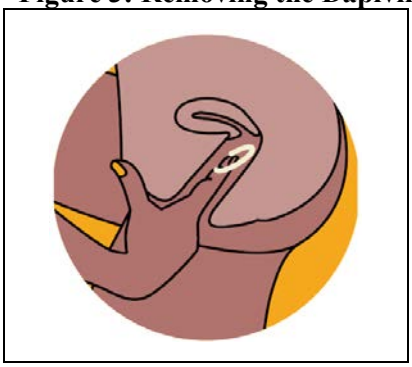
Figure 2: Inserting the Dapivirine Vaginal Ring



- Hold the Dapivirine Vaginal Ring between your thumb and index finger, twisting it into the shape of the number eight (8) or pressing the sides together (Figure 2A).
- Use the other hand to hold the folds of the skin around the vagina open.
- Place the tip of the vaginal ring into the vagina opening (Figure 2B).
- Use the index finger to gently push the folded vaginal ring into the vagina as far as possible (Figure 2C).
- If the ring feels uncomfortable, it may not have been pushed far enough into the vagina. Try again to gently push it into the vagina as far as possible, or remove and reinsert it. Please note: The ring *cannot* be pushed up too far or get lost in the body.
- If it still feels uncomfortable, contact your healthcare provider.
- Wash your hands in clean water and dry them.

Replacement

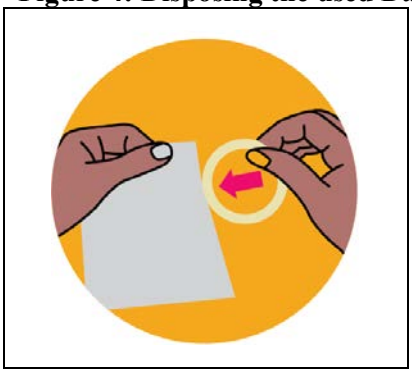
Figure 3: Removing the Dapivirine Vaginal Ring



- Remove the vaginal ring one month from the day it was inserted.
- Wash your hands in clean water and dry them.
- Choose a comfortable position with legs apart.
- Use your finger to hook the vaginal ring and gently pull it out of your vagina (Figure 3).
- Immediately insert a new Dapivirine Vaginal Ring, following the instructions for insertion (Figure 2).

Disposal

Figure 4: Disposing the used Dapivirine Vaginal Ring



- Place the used vaginal ring inside an empty pouch (Figure 4), or wrap it in tissue or toilet paper.
- Dispose the used vaginal ring in the rubbish bin and out of reach of children.
- Do not dispose the vaginal ring in the toilet.
- Wash your hands in clean water and dry them.

If the Dapivirine Vaginal Ring accidentally falls out or is removed

Your Dapivirine Vaginal Ring may accidentally fall out e.g. when you go to the toilet or during vaginal intercourse, or be accidentally removed, e.g. when you remove a tampon.

If this occurs in a place that is not dirty (e.g. in the bed or in the clothes)

- Rinse the Dapivirine Vaginal Ring in clean water.
- Immediately re-insert the Dapivirine Vaginal Ring as described above.

If the Dapivirine Vaginal Ring has touched something dirty (e.g. the toilet):

- Do not re-insert the vaginal ring.
- Discard the vaginal ring as described above.
- Insert a new vaginal ring as described above.

If you use more Dapivirine Vaginal Rings than you should

If you realize you have more than one ring in your vagina, remove all rings and insert a new ring immediately. Do not use any of the rings that you have just removed.

If you keep the ring in the vagina for longer than one month

If you realize that you have kept the ring in the vagina for longer than one month, replace with a new ring immediately.

If you forget to use the Dapivirine Vaginal Ring

Insert a new vaginal ring immediately. Do not insert two rings.

Do not stop using Dapivirine Vaginal Ring

While you are using the Dapivirine Vaginal Ring, to reduce the chance of getting HIV-1 infected, do not stop or interrupt using the ring and do not miss any monthly ring replacements. Stopping the use of the ring, or missing the monthly replacement, may increase your chance of getting HIV-1 infection.

Do not stop using the Dapivirine Vaginal Ring without talking to your healthcare provider

If you have any further questions on the use of the Dapivirine Vaginal Ring, ask your healthcare provider.

If you remove the ring, your chance of getting HIV-1 infection is not reduced.

You must talk to a healthcare provider if you have signs of HIV infection (listed in section 2) when using the Dapivirine Vaginal Ring.

4. Possible side effects

Like all medicines, the Dapivirine Vaginal Ring can cause side effects, although not everybody gets them.

Very common side effects (may affect **more than 1 in 10 people**):

- Urinary tract infection

Common side effects (may affect **up to 1 in 10 people**):

- Inflammation (swelling, redness and pain) of the vagina and/or the area outside the vagina (vulva),
- Inflammation of the lower part of the womb (cervix),
- Discharge from the vagina,
- Itching of the vagina and/or the area outside the vagina (vulva),
- Pain in the lower part of the belly (abdomen, pelvis),
- Pain or difficulty in passing urine

Uncommon side effects (may affect **up to 1 in 100 people**):

- Inflammation of the bladder,
- Smell from the vagina,
- Redness or swelling of the lower part of the womb (cervix),
- An uncomfortable feeling of the vagina and/or the area outside the vagina (vulva),
- Pain in the vagina and/or the area outside the vagina (vulva),
- Discharge from the lower part of the womb (cervix),
- Bruising or small spots of internal bleeding of the lower part of the cervix,
- An uncomfortable feeling in the lowest part of the belly (pelvis),
- A sore (ulceration) in the vagina or the lower part of the womb (cervix),
- Passing of urine more often than normally,
- Pain in the bladder,
- Pain in the area below the belly button (navel),
- An uncomfortable feeling at the location where the ring is placed,
- A cut in the vagina

Rare side effects (may affect **up to 1 in 1,000 people**):

- An uncomfortable feeling in the belly,
- An uncomfortable feeling or itching of the genitals,
- An area of the skin which is scraped away in the vulva (vulval abrasion),
- A feeling that you need to pass urine urgently,
- Pain at the location where the ring is placed.

Reporting of side effects

If you get any side effects, talk to your healthcare provider. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Dapivirine Vaginal Ring

Keep this medicine out of the sight and reach of children.

Store in the original package in order to protect from light.

Do not open the package until the moment you are going to insert the Dapivirine Vaginal Ring.

Do not throw away the Dapivirine Vaginal Ring in the toilet or water drains. Throw the used ring in a rubbish bin out of the reach of children.

6. Contents of the pack and other information

What Dapivirine Vaginal Ring contains:

The active substance in the Dapivirine Vaginal Ring is dapivirine. Each ring contains 25 mg of dapivirine.

The other inactive ingredients are:

Dimeticone, 1,000 centistokes (cSt)
Silicone Elastomer (DDU-4870):
- Siloxanes and Silicones, dimethyl, vinyl group-terminated
- Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane
- Silica, amorphous, fumed, crystalline free
- Siloxanes and silicones, dimethyl, methyl vinyl, methyl hydrogen, hydroxyl-terminated

What the Dapivirine Vaginal Ring looks like and the contents of the pack

The Dapivirine Vaginal Ring is a ring that is designed to release a medicine in the vagina. It can easily bend, has an off-white colour and is made of silicone material with an outer diameter of 56 mm and a cross-sectional diameter of approximately 8 mm.

Each Dapivirine Vaginal Ring is packaged into a laminated (PET-Alu/Adhesive/PP), square, heat-sealed pouch. A carton contains either one pouch or three pouches.

Scientific Opinion Holder

International Partnership for Microbicides Belgium (IPM Belgium) AISBL
Square de Meeûs 38/40
1000 Brussels
Belgium

Manufacturer

QPharma AB
Agneslundsvägen 27
Malmö Sweden

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: **http://www.ema.europa.eu.**