Professional information for DapiRing

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DapiRing 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 DapiRing is inserted into the vagina and kept in until replaced every 28 days with a new ring. To maintain efficacy, a new DapiRing should be inserted immediately after the previous ring is removed.

The DapiRing must be used as directed (see “Method of administration”). If the DapiRing is

accidentally expelled or removed, the woman should follow the instructions given below under "*Accidental expulsion or removal of the DapiRing*".

Special populations

Paediatric population

The safety and efficacy of the DapiRing 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 DapiRing

The woman should wash her hands in clean water and dry them before removing the DapiRing from the package.

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

Figure 1: Positioning for Inserting the DapiRing

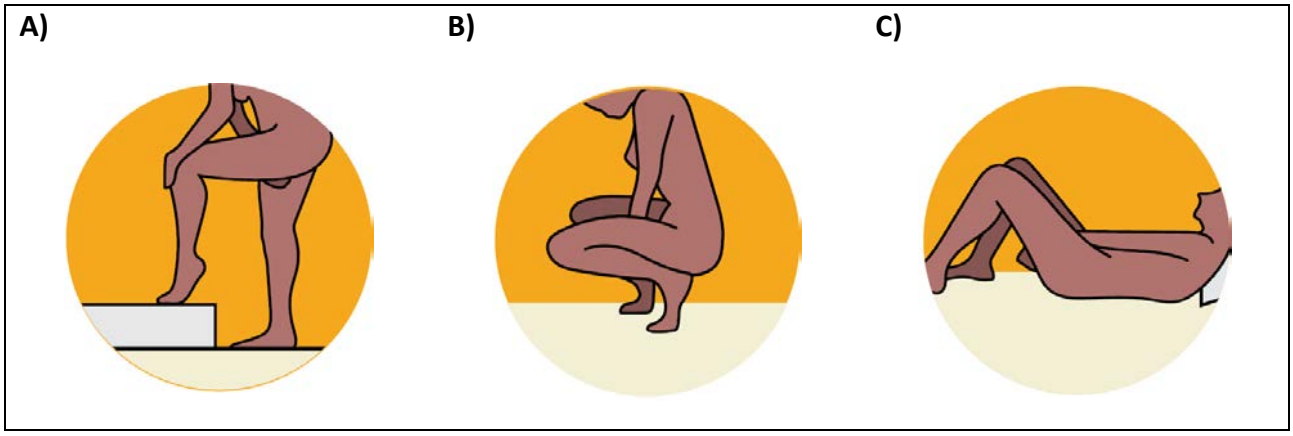
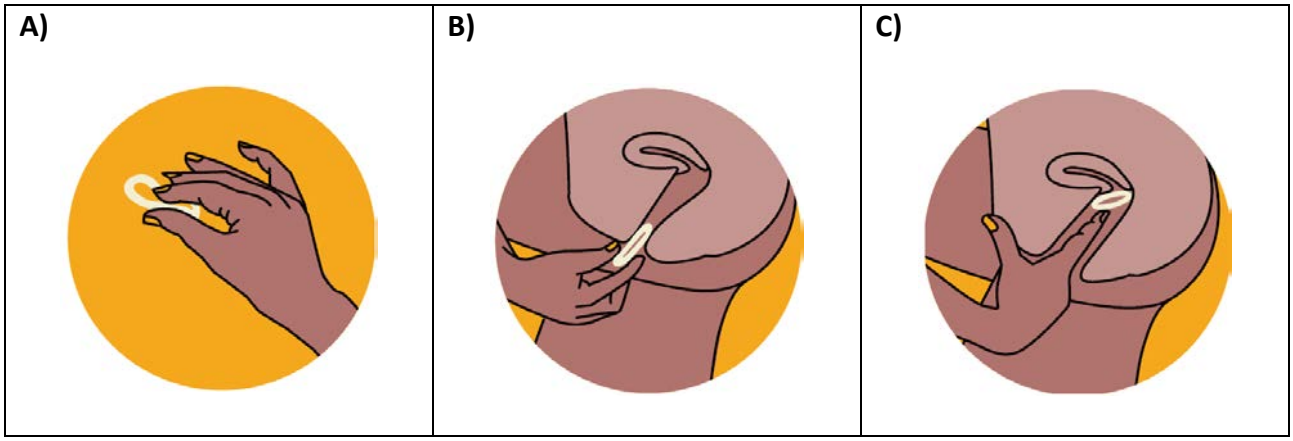
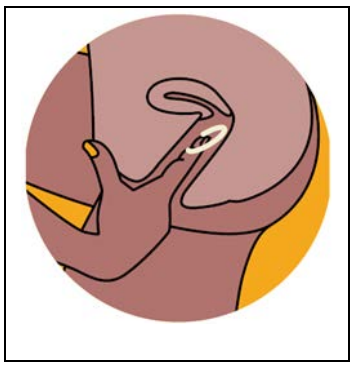


Figure 2: Inserting the DapiRing



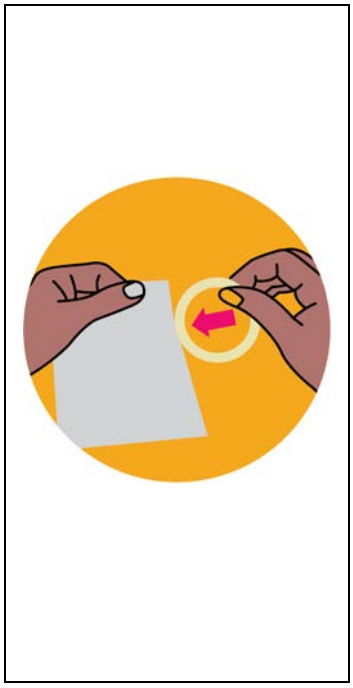
The DapiRing should be held between the thumb and index finger, twisting it into the shape of the number eight (8) or pressing the sides together (Figure 2A). Using the other hand, the folds of the skin around the vagina should be held open. The tip of the ring should be placed in the vagina opening (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 DapiRing



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 DapiRing



To dispose the used DapiRing, 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 DapiRing

The DapiRing may be accidentally expelled (e.g. during a bowel movement, urination, menses or vaginal intercourse) or removed (e.g. when removing a tampon).

The woman may check if the DapiRing is still in the vagina if she is unsure whether it may have been accidentally expelled. She should follow the instructions for ring removal (Figure 3) to either remove the ring and immediately reinsert it (Figure 2) or choose a comfortable position and insert her index finger into the vagina to feel if the ring is still in place.

If accidental expulsion/removal occurs in a clean environment (e.g. whilst in bed or inside clean clothing), and the DapiRing 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 DapiRing 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 DapiRing (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 DapiRing 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 DapiRing should only be used as part of an overall HIV-1 infection prevention strategy, including the use of other HIV-1 prevention measures, which include consistent and correct condom use and regular testing for other sexually transmitted infections.

The DapiRing is used locally in the vagina and only reduces the risk of HIV-1 infection in women by vaginal intercourse.

The DapiRing should not be removed prior to, during or after vaginal sexual intercourse.

Risk of HIV resistance with undetected HIV-1 infection

The DapiRing 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 DapiRing (see section 4.3).

Continued use of the DapiRing 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 DapiRing should be delayed or stopped for at least one month and HIV-negative status should be confirmed before initiating or continuing the use of the DapiRing.

Importance of adherence to product use

Women using the DapiRing should be counselled to strictly adhere to the recommended continuous use of the ring and to replace it every 28 days.

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 DapiRing 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 DapiRing 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 DapiRing 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 DapiRing. Therefore, concomitant use of such practices with the DapiRing is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Due to the low systemic exposure to dapivirine in women using the DapiRing, which does not exceed 2 ng/mL (see section 5.2), the risk of systemic medicine interactions is considered low and medicine interaction studies were focused on medicines 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). Dapivirine inhibited several CYP450 and UGT enzymes (see section 5.2), and therefore there is the potential for interactions, specifically in the vaginal tissues, with co-administered vaginal medicines that are metabolised by

these enzymes.

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 1 200 mg miconazole, administered as an oil-based formulation in a vaginal capsule, with the DapiRing was evaluated in a single clinical trial.
Under these circumstances miconazole concentrations in vaginal fluids were approximately 6-fold higher and miconazole concentrations in plasma were 4-fold higher following co-administration. While these changes are explained by the inhibitory potential of dapivirine towards the metabolism of miconazole (via CYP3A4), these changes are not considered clinically relevant.
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 did not change significantly. The underlying mechanisms are not fully resolved and clinical relevance is unclear. Even so, 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 DapiRing 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 DapiRing 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 DapiRing with such products is not recommended.

Other forms of interactions

Use with condoms

The DapiRing can be used with condoms and both should be used during vaginal sexual intercourse.

Clinical data show that the use of the DapiRing 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 DapiRing 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 DapiRing 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 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 DapiRing 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 DapiRing 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 DapiRing (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.

Lactation

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 (< 1 420 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 DapiRing. 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 DapiRing 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 DapiRing (see section 5.3).

4.7 Effects on ability to drive and use machines

The DapiRing 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 reactions (i.e. reported by ≥ 5 % of participants in the DapiRing 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 reactions observed in the clinical trials with the DapiRing, 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 < 1/1 000).

Table 1: Tabulated summary of adverse reactions associated with the DapiRing, 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 DapiRing 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 odour, 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 DapiRing 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 DapiRing group and 23 participants to the placebo ring group. The DapiRing was well tolerated in adolescent females when inserted once every 4 weeks and used continuously for 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 DapiRing is important. It allows continued monitoring of the benefit/risk balance of DapiRing. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The potential for overdose using the DapiRing 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

Category and class: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Gynaecological 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 DapiRing and placebo ring groups had NNRTI mutations identified in samples taken soon after HIV-1 infection (IPM 027: DapiRing: 16/84, 19,0 %; placebo ring: 8/58, 13,8 %; MTN-020: DapiRing: 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 DapiRing 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 DapiRing-exposed participants in either of the Phase III clinical trials. Five participants in the DapiRing group in IPM 027 had HIV-1 infection prior to enrolment. Four participants had genotypic testing at enrolment, 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 DapiRing group and the placebo ring group. There were more participants with more than one NNRTI resistance-associated mutation in the DapiRing group in the MTN-020 trial (7,3 % [5/68] of participants in the DapiRing 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 DapiRing).

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 DapiRing 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 DapiRing 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 DapiRing 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 DapiRing continuously following insertion and replace it with a new DapiRing 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 DapiRing was assessed by comparing the risk of HIV-1 infection between the DapiRing and the placebo ring groups. The primary efficacy analysis, based on data as of a cut-off date of 16 October 2015, showed that DapiRing 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 DapiRing in Phase III clinical trial IPM 027: Primary analysis (Cut-off date 16 October 2015) – Modified intent-to-treat population

	DapiRing	**Placebo Ring**	**DapiRing vs Placebo Ring**
Number of participants in m-ITT population[a]	1 302	650	
Number of confirmed trial endpoints[b]	80 (6,1 %)	59 (9,1 %)	
Number of censored values[b,c]	1 222 (93,9 %)	591 (90,9 %)	
Total person years of follow-up	1 889	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 enrolment

[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 DapiRing	**Non-Adherent DapiRing**	**Placebo Ring**	**Adherent DapiRing vs Placebo Ring**	**Non-Adherent DapiRing vs Placebo Ring**
Number of confirmed trial	54	26	59		

endpoints					
Number of censored values[a]	897	308	591		
Total person years of follow-up[b]	1 454	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 enrolment.

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)	93/2 150	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 enrolment.

[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 DapiRing in women under the age of 18 years has not been established.

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 DapiRing 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 DapiRing for 28 days and after removal of the Ring on day 28 (IPM 028)

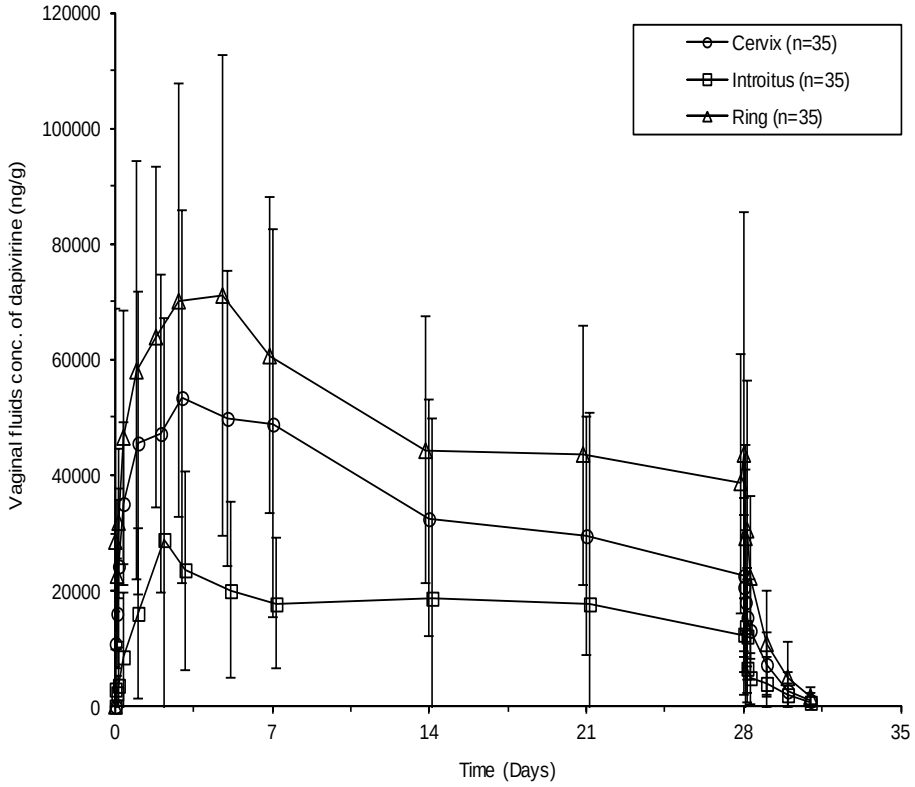


Figure 5B: Mean (SD) dapivirine concentrations in plasma following continuous use of the DapiRing for 28 days and after removal of the Ring on day 28 (IPM 028)

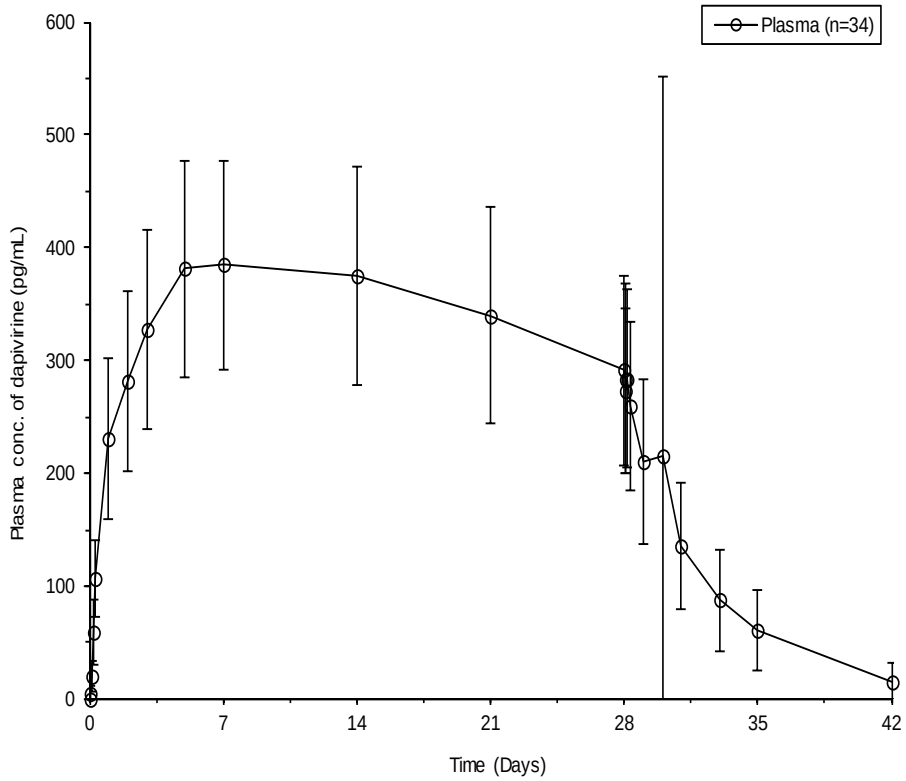


Table 5: Dapivirine pharmacokinetic parameters in vaginal fluid (cervix) and plasma during use of the DapiRing for 28 days (IPM 028)

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
$AUC_{0\text{-}28days}$	229 408 (57 399) pg,h/mL	24 222 (10 476) 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 DapiRing were highly variable (ranging from 46 – 12 900 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. Dapivirine is a substrate of CYP1A1 and CYP3A4 enzymes, but is not a substrate of CYP1A2, CYP1B1, CYP2B6, CYP2C8 or

CYP2C19, or of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9 or UGT2B7.

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.

Dapivirine was not a substrate of drug transporters P-gp, BCRP, MRP1, MRP4, and ENT1 in vitro at concentrations observed in the vaginal fluid and had no inhibitory effects on the activity of these transporters at maximal vaginal concentrations and maximal plasma concentrations.

In vitro dapivirine showed varying degrees of inhibition of CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4.

At maximal plasma concentrations, dapivirine is not an inhibitor of UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9 and 2B7. In vaginal tissue no UGT enzyme activity was detected.

Dapivirine was not an inducer via AhR (CYP1A2), CAR (CYP2B6) and PXR (CYP3A4) at 0,3 µM (0,1 µg/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 DapiRing 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 keratinised 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 1 000-fold within hours after ring insertion and by more than 3 000-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 > 3 000-fold (at the introïtus) and > 6 000-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 DapiRing 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 DapiRing.

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 1 000-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 1 000-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 1 000-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

60 months.

Store at or below 30 °C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Each DapiRing is packaged into a laminated (PET-Alu/Adhesive/PP), square, heat-sealed pouch.

A carton contains either one pouch (1 ring) or three pouches (3 rings).

6.6 Special precautions for disposal and other handling

Do not use if the seal on the pouch is broken.

Do not flush used or unused product.

Do not throw away the DapiRing in the toilet or water drains. The used DapiRing 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor,

10 Church Street,

Durbanville, 7551

8. REGISTRATION NUMBER

55/20.2.8/0786

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 March 2022

10. DATE OF REVISION OF THE TEXT