PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR DAPIVIRINE VAGINAL RING (DAPIVIRINE)

This is a summary of the RMP for the Dapivirine Vaginal Ring. The RMP describes important risks that a women may experience while using the Dapivirine Vaginal Ring. The plan explains how these risks can be minimised, and how more information will be collected to better understand the risks and unknown effects caused by use of the Dapivirine Vaginal Ring.

This summary of the RMP for the Dapivirine Vaginal Ring should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

A Patient Information Leaflet and User Guide containing information about the safe use and possible side effects is provided to women who decide to use the Dapivirine Vaginal Ring.

Healthcare professionals will also receive more detailed information to guide the appropriate use in those women who decide to use the Dapivirine Vaginal Ring. This guide will be adapted for the different countries where the Dapivirine Vaginal Ring is marketed (HCP Guide – country specific).

I THE MEDICINE AND WHAT IT IS USED FOR

The medicine contained in the vaginal ring is called dapivirine. This medicine makes it more difficult for the most common form of the HIV, HIV-1, to multiply inside human cells and so prevents HIV infection during vaginal sex. It is intended to be used in sexually-active women, who are 18 years of age and older, and who also use safer sex practices. The Dapivirine Vaginal Ring is placed inside the vagina where the dapivirine is slowly released. Only small amounts of dapivirine are absorbed into the blood and rest of the body.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Risks that have already been identified or possible risks that may be due to use of the Dapivirine Vaginal Ring and what steps will be taken to limit these risks as far as possible, as well as what will be done to better understand these risks, are described below.

Steps that can be taken to limit these risks are:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet for users of the Dapivirine Vaginal Ring, and a document called the SmPC which is intended for HCPs.
- Important advice on the medicine's packaging.
- The authorised pack size – the amount of medicine in a pack is chosen to make sure that the medicine is used correctly.
- The medicine's legal status – for example, whether a prescription is needed to get the medicine.

The points mentioned above describe the standard (routine) steps that, when taken together, help to reduce (minimise) risks when using the Dapivirine Vaginal Ring (routine risk minimisation measures).

Additional measures to minimise risks are described in the section below as additional risk minimisation measures.

The additional risk minimisation measures will include the use of educational materials such as an HCP and a User Guide to promote adherence to correct product use and to minimise any potential harm.

The HCP Guide will provide educational information to HCPs on the correct use of the product, explain what information is unknown and any risks associated with the product. The information is also provided to help the HCP to counsel a potential user and if applicable, her partner(s).

The HCP Guide will explain the following key points which can be used during counselling of users:

- 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 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 User Guide is an educational material developed for the ring user and will instruct her and her partner(s), if applicable, on how to properly use the Dapivirine Vaginal Ring and mention the relevant safety concerns associated with the product. Key messages in the User Guide can also be used by the HCP during counselling of a prospective vaginal ring user.

The following information will be included:

- 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 (e.g., 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 (e.g., 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 (e.g., 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.

Additionally, the User Guide will provide information on what to do if the user thinks she may be HIV infected and what the signs and symptoms are of early HIV infection, as well as what to do if she suspects she may be pregnant or wishes to become pregnant. Testing of a user's understanding on how to use the product correctly will be undertaken from time to time.

If important information about the safe use of the Dapivirine Vaginal Ring is not yet known or available, it is listed under "missing information" below.

In addition, several sources of information are regularly reviewed to look for reports of "side effects" or "adverse reactions" in women who are using the Dapivirine Vaginal Ring. Any safety issues in connection with the Dapivirine Vaginal Ring are assessed, and if necessary, immediate action can be taken, in addition to usual activities to ensure the safe use of the product. These activities are called routine PV activities.

II.A List of Important Risks and Missing Information

Important risks of the Dapivirine Vaginal Ring are risks that users (and their partners, if applicable) should be aware of. Risks may be considered important identified or potential risks. Identified risks are risks for which there is enough proof of a link between the risk and the use of the Dapivirine Vaginal Ring. Potential risks are risks for which there is not enough proof of a link and therefore further information should be collected to better understand the risk.

The most important identified risk is becoming HIV-1 infected because of incorrect use of the Dapivirine Vaginal Ring and not using it in combination with other safer sex practices.

It is also important to understand that not everything is known about the Dapivirine Vaginal Ring. Information that was not collected before and may need to be collected is considered missing information.

Potential risks and missing information include the following:

- Developing resistance to this type of medicine and medicines closely related to it. If women continue to use the Dapivirine Vaginal Ring after unknowingly becoming infected with HIV-1, the HIV in the body may undergo changes and may make other medicines that are used to treat HIV infection less effective, (potential risk).

- The possibility of developing an infection in the lower belly (pelvic region) if there is an unrecognized infection in the vagina which is not treated soon enough, (potential risk).
- How safe the medicine is when used by women who are pregnant or breastfeeding, (missing information).
- Long-term use of the Dapivirine Vaginal Ring beyond 24 months of treatment, (missing information).
- Use of the Dapivirine Vaginal Ring in women younger than 18 years of age, (missing information).
- Whether the use of other vaginal medicines (such as clindamycin and metronidazole) together with the Dapivirine Vaginal Ring affects either medicine or causes side effects because these medicines are used at the same time.

Table II-1: Lists of Important Risks and Missing Information

List of important risks and missing information	
Important identified risks A risk that has adequate proof (evidence) of being linked to the Dapivirine Vaginal Ring and could affect the balance between the benefit of using the Dapivirine Vaginal Ring compared with experiencing the risk	The risk of becoming infected with HIV-1 if the Dapivirine Vaginal Ring is not used properly and is not used in combination with safer sex practices.
Important potential risks A risk where there is a suspicion but no confirmation of a link between the risk and the use of the Dapivirine Vaginal Ring that could affect the balance between the benefit of using the Dapivirine Vaginal Ring versus experiencing the risk	• Developing resistance to this type of medicine and medicines closely related to it. If continuing to use the Dapivirine Vaginal Ring after unknowingly becoming infected with HIV-1, the virus may undergo changes and may make other medicines that are used to treat HIV infection less effective. • The possibility of developing an infection in the lower belly (pelvic region) if an infection in the vagina is not treated soon enough.
Missing information Information about use of the Dapivirine Vaginal Ring which is not yet well understood	• How safe the medicine is when used in women who are pregnant or breastfeeding. • How safe the medicine is when used long-term beyond 24 months. • Use of the Dapivirine Vaginal Ring in women younger than 18 years of age is limited. • Whether the use of other vaginal medicines (such as clindamycin and metronidazole) together with the Dapivirine Vaginal Ring affects either medicine or causes side effects because these medicines are used at the same time.
HIV-1 = human immunodeficiency virus type 1	

II.B Summary of Important Risks

Table II-2: Summary of important risks and missing information

Summary of important risks and missing information	
Important identified risk: HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use	
Evidence for linking the risk to the medicine Clinical studies have showed that if you use the Dapivirine Vaginal Ring correctly, the risk of becoming infected with HIV-1 is less.	The Dapivirine Vaginal Ring does not prevent HIV-1 infection in all of the women who use the Dapivirine Vaginal Ring. Clinical studies showed that the Dapivirine Vaginal Ring prevented HIV-1 infection in approximately 30% of all women who participated in those trials, and in women older than 21 years of age the Dapivirine Vaginal Ring prevented HIV-1 infection in 42.9%. There are several possible reasons for this result, including not using the Dapivirine Vaginal Ring all the time as instructed and not using additional safer sex practices. The Dapivirine Vaginal Ring does not protect against STIs other than HIV-1. Safer sex practices will protect against other STIs. Furthermore, it is unknown if an untreated STI will reduce the ability of the Dapivirine Vaginal Ring to protect against HIV-1 infection. It is also unknown what effect the use of products to clean the vagina or prepare the vagina before sexual activity (vaginal practices) can have on the Dapivirine Vaginal Ring, and whether this would make the medicine less effective in preventing HIV-1 infection, therefore, it is not recommended to use such practices when using the Dapivirine Vaginal Ring.
Risk factors and risk groups	In general, all users who do not use the Dapivirine Vaginal Ring as instructed will have less protection from getting HIV-1 infection when having vaginal sex. Women between 18 and 21 years of age: Some clinical trials found that the Dapivirine Vaginal Ring did not show the same level of protection from HIV-1 infection for women between 18 and 21 years of age when compared to older women. While there are no known differences in how the Dapivirine Vaginal Ring works in different age groups, the reduced effect of the Dapivirine Vaginal Ring seen in the younger group may be because they were less likely to use the Dapivirine Vaginal Ring correctly, and were also less likely to practice safer sex, since these trials did show that women between 18 and 21 years of age experienced STIs more frequently than older women. It is not known if women who used the Dapivirine Vaginal Ring during clinical trials felt comfortable that it would protect them and therefore took more risks by not also using safer sex practices. These younger women might also engage in vaginal practices and use vaginal medicines to treat vaginal infections.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Sections 4.1, 4.2 and 4.4. Advice will be provided in the Patient Information Leaflet, Sections 2 and 3, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to provide guidance on the best way to use the Dapivirine Vaginal Ring in order to reduce the users' chance of becoming HIV-1 infected.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Important potential risk: Development of non-nucleoside reverse transcriptase inhibitor resistance in women with unrecognized or acute HIV-1 infection	
Evidence for linking the risk to the medicine	It is currently not known for sure whether using the Dapivirine Vaginal Ring in HIV-1 infected women, increases the chance of the HIV-1 virus changing form

Summary of important risks and missing information	
	(mutating), and thereby possibly making other similar medicines used to treat HIV infection, less effective (development of NNRTI resistance). Results from completed trials showed that apart from one type of NNRTI mutation (namely the E138A mutation), which was higher in the group of women exposed to the Dapivirine Vaginal Ring, the percentage of women who became HIV-1 infected and had any type of NNRTI mutation was similar in women who used the Dapivirine Vaginal Ring or the placebo ring. Additionally, there was a small number but a higher percentage, of women who received the Dapivirine Vaginal Ring who had more than one NNRTI mutation. Overall, the available data suggest a low risk for the Dapivirine Vaginal Ring to cause such changes in the virus. These differences would seem more likely to be due to changes already present in HIV-1 when women were infected however the possibility they may be caused by continuing to use the Dapivirine Vaginal Ring after becoming HIV-1 infected cannot be completely excluded.
Risk factors and risk groups	Women who could potentially be at higher risk are those using the Dapivirine Vaginal Ring and not knowing they are already HIV-1 infected, including those women who do not undergo regular testing to confirm that they are still HIV-negative.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.4. Advice will be provided in the Patient Information Leaflet, Section 2, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to reduce the chances of developing NNRTI mutations.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: IPM 032 (DREAM) and MTN-025 (HOPE) These two additional trials collected information on the number and percentage of women who used the Dapivirine Vaginal Ring and become HIV infected, and who develop mutations associated with resistance to the class of ARV drugs that dapivirine belongs to, the so called NNRTIs. Information on the type of mutations was also collected and what these mutations might mean when receiving future HIV treatment. IPM 007 and MTN-015 observational cohort studies: Participants in the completed IPM 027 and MTN-020 trials who became infected with HIV-1 while in the trial, and participants in the follow on IPM 032 and MTN-025 trials who become HIV-1 infected while in the trial, will be able to participate in these trials. These trials collected information to assess if using the Dapivirine Vaginal Ring at the time of HIV-1 infection could have an effect in the way in which other medications used to treat HIV are able to control the HIV infection after these medications are prescribed as treatment for HIV infection. These trials also collected information about how the HIV infection progresses based on physical condition, and on results of certain laboratory tests. Comparisons will be made in the results of women who were using the Dapivirine Vaginal Ring compared to women who used a ring without any dapivirine (placebo ring). Final results from these trials suggest little impact of previous use of the Dapivirine Vaginal Ring on the response to HIV treatment when compared to the treatment response rates of women who had used a placebo vaginal ring previously. Additionally, no clear pattern of mutations (changes in the virus) was observed to be favoured after using the Dapivirine Vaginal Ring.
Important potential risk: Development of pelvic inflammatory disease	

Summary of important risks and missing information	
Evidence for linking the risk to this medicine	The percentage of women who developed PID who had used the Dapivirine Vaginal Ring in clinical trials was low. Most women who developed PID could be successfully treated and continue using the Dapivirine Vaginal Ring. What is not known is, if a woman has an infection in her vagina and does not receive treatment for it and then continues to use the Dapivirine Vaginal Ring, whether the fact that she has the Dapivirine Vaginal Ring in her vagina can lead to the infection spreading higher up into her belly causing PID.
Risk factors and risk groups	Risk factors for development of PID include, multiple sexual partners, a history of STIs, a history of sexual abuse, recent medical procedures involving the womb or vagina, and use of contraceptive devices in the womb. Younger women may also be at higher risk due to differences in their vaginas when compared to older women, and possibly due to taking more risks in their sexual behaviour.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.4. Advice will be provided in the Patient Information Leaflet, Section 2, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to minimise the chances of getting PID, and provide advice on symptoms to look out for to assist with early recognition and treatment should a Dapivirine Vaginal Ring user develop PID.
Additional pharmacovigilance activities	None
Important missing information: Safety during pregnancy	
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.6. Advice will be provided in the Patient Information Leaflet, Section 2, for women who plan to become pregnant or may fall pregnant while using the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to make the best possible decision regarding the use of the Dapivirine Vaginal Ring during pregnancy. There is limited information on the use of the Dapivirine Vaginal Ring in pregnant women. As a precaution, it is preferred that the use of the Dapivirine Vaginal Ring during pregnancy is avoided, unless the healthcare provider considers that the woman (and possibly the unborn child too) is at high risk of HIV-1 infection.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MTN-016 (EMBRACE) Women who became pregnant in the MTN-020 and MTN-025 trials and who joined this study will have data collected on their pregnancy outcomes as well as their infant growth and development until 12 months of age, for all pregnancies with an outcome of a live birth. The results of this study showed that pregnancy outcomes were similar between women who had used the Dapivirine Vaginal Ring compared to a placebo vaginal ring. Additionally, infant growth that was assessed up to the age of one year showed no difference in infants born to mothers who had used the Dapivirine Vaginal Ring compared to the placebo vaginal ring. MTN-042 (DELIVER)

Summary of important risks and missing information	
	This trial is ongoing and will collect safety information and monitor the way in which dapivirine is metabolized (absorbed, broken down, and removed from the body) in pregnant women. This trial will randomly select pregnant women to receive either the Dapivirine Vaginal Ring or an oral tablet that is used to prevent HIV infection.
Important missing information: Safety during breastfeeding	
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.6. Advice will be provided in the Patient Information Leaflet, Section 2, for women who plan to breastfeed while using the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to make the best possible decision regarding the use of the Dapivirine Vaginal Ring during breastfeeding.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MTN-043 (B-PROTECTED) This trial is ongoing and will assess the way in which the body metabolizes dapivirine (absorbs, breaks down, and removes dapivirine from the body) in women using the Dapivirine Vaginal Ring during breastfeeding. Participants for this trial will be HIV-negative breastfeeding women who have healthy infants and who are willing to use the Dapivirine Vaginal Ring for approximately 12 weeks. Special tests will be taken during the trial to assess the safety and the way in which the body metabolizes dapivirine.
Important missing information: Long-term use beyond 24 months of treatment	
Risk minimisation measures	Routine risk communication: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: IPM 032 (DREAM) A review of safety data from a group of women who participated in the IPM 027 trial and who immediately continued in the IPM 032 trial without any interruption of the Dapivirine Vaginal Ring, and therefore used the ring for continuously for more than 24 months did not identify any new safety concerns.
Important missing information: Use in sexually-active females under 18 years of age	
Risk minimisation measures	Routine risk communication: Information will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Sections 4.1, 4.2, and 5.1. Information will be provided in the Patient Information Leaflet, Section 2.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MTN-034 (REACH) This trial will assess if the Dapivirine Vaginal Ring is safe and acceptable to younger women and whether or not the investigational products are used correctly. Women will use the Dapivirine Vaginal Ring (25 mg dapivirine) and oral PrEP tablet (TDF/FTC), at different times and then after using each product they will indicate which of the two products they prefer to use during a third period of product use, or may decide not to use anything during this third part of the trial. Healthy African, HIV-negative, sexually-active adolescent and young adult women between the ages of 16 to 21 years of age will participate

Summary of important risks and missing information	
	in the trial In this trial, participants will receive the Dapivirine Vaginal Ring or take the oral PrEP tablet (TDF/FTC) for a period of 6 months at a time.

Summary of important risks and missing information	
Important missing information: Local drug-drug interaction with clindamycin and metronidazole	
Risk minimisation measures	Routine risk communication: Information will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.5. Information will be provided in the Patient Information Leaflet, Section 2. Information will be provided in a Healthcare Professional Guide and a User Guide to indicate that there is currently no information on the use of either clindamycin or metronidazole when used in the vagina at the same time as the Dapivirine Vaginal Ring. Users will be reminded to contact their clinic or doctor before using any vaginal medicines at the same time as the Dapivirine Vaginal Ring.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
ARV = antiretroviral; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; PID = pelvic inflammatory disease; PrEP = pre-exposure prophylaxis; TDF = tenofovir disoproxil fumarate; STI = sexually transmitted infection	

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Study short name: Implementation Study

Purpose of the study: Given uncertainties regarding the efficacy of the Dapivirine Vaginal Ring in younger women, this study will assess uptake, and persistence of use over a 12-month period. Additionally, the HIV-1 seroconversion rate will be described. Analyses will be stratified by two age categories, 18-21 years and > 21 years to 25 years. Qualitative assessments of barriers to uptake, adherence, and persistence will be described.

II.C.2 Other Studies in Post-authorisation Development Plan

Study short name: MTN-034 (REACH)

Purpose of the study: To compare the safety profiles, adherence to and acceptability of FTC/TDF oral tablet administered daily and the Dapivirine Vaginal Ring-004 inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population. Additionally, the trial will compare participant preference between the Dapivirine Vaginal Ring-004 and FTC/TDF oral tablets over the course of study and study product adherence during the third study product use period when preferred study product is chosen against the study product use period during which the study product is randomly assigned.

Study short name: MTN-042 (DELIVER)

Purpose of the study: To describe the maternal and infant safety profile associated with study product (Dapivirine Vaginal Ring-004 or FTC/TDF) exposure during pregnancy and describe the pregnancy outcomes and pregnancy complications associated with such exposure during pregnancy. Additionally, infant levels of study drugs associated with study product exposure during pregnancy will be described and adherence and acceptability to use of either study product will be described.

Study short name: MTN-043 (B-PROTECTED)

Purpose of the study: To describe the maternal and infant safety profile associated with study product exposure during breastfeeding in both study arms, (Dapivirine Vaginal Ring-004 or FTC/TDF). Additionally, the frequency

of study drug detection and concentration of study drug(s) in mothers and their breastfeeding infants will be summarized, as well as the willingness of breastfeeding women to use either product, and adherence to the study product will be characterised.