Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for levonorgestrel (all indications except emergency contraception), the scientific conclusions are as follows:

In view of available data from the literature, on the risk of masculinisation of female foetus when the levonorgestrel intra-uterine device remains during pregnancy and in view of a plausible mechanism of action, the PRAC considers a causal relationship between levonorgestrel-containing intra-uterine devices and masculinisation of female foetus when levonorgestrel-containing intra-uterine devices remain during pregnancy is at least a reasonable possibility. The PRAC concluded that the product information of products containing levonorgestrel intra-uterine devices should be amended accordingly.

Furthermore, in view of available data from a post-authorisation safety study on the risk of levonorgestrel intra-uterine device expulsion in women with heavy menstrual bleeding and with a higher than normal body mass index (BMI), the PRAC considers a causal relationship between levonorgestrel-containing intra-uterine devices and a higher expulsion rate in women with a history of heavy menstrual bleeding and higher than normal body mass index (BMI) is at least reasonable possibility. The PRAC concluded that the product information of products containing levonorgestrel intra-uterine devices should be amended accordingly.

The product information of products containing levonorgestrel intra-uterine devices are to be amended in full accordance with the already finalised procedures SE/H/xxxx/WS/406 and SE/H/xxxx/WS/450.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for levonorgestrel (all indications except emergency contraception) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levonorgestrel (all indications except emergency contraception) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing levonorgestrel (all indications except emergency contraception) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike-through~~)

Summary of Product Characteristics

- Section 4.4

The existing warning should be amended as follows:

Expulsion

In clinical trials with [brand name] in the indication contraception, the incidence of expulsion was low (<4% of insertions) and in the same range as reported for other IUDs and IUSs. Symptoms of ~~**the**~~ partial or complete expulsion of ~~**any IUD**~~ **[brand name]** may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it, leading to loss of contraceptive protection. ~~**Partial expulsion may decrease the effectiveness of [brand name]**~~ As [brand name] decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

Risk of expulsion is increased in

- **Women with history of heavy menstrual bleeding (including women who use [brand name] for treatment of heavy menstrual bleeding)**
- **Women with greater than normal BMI at the time of insertion; this risk increases gradually with increasing BMI**

Woman should be counselled on possible signs of expulsion and how to check the threads of [brand name] and advised to contact a healthcare professional if the threads cannot be felt. A barrier contraceptive (such as a condom) should be used until the location of [brand name] has been confirmed.

Partial expulsion may decrease the effectiveness of [brand name].

A ~~**displaced**~~ **partially expelled** [brand name] should be removed. A new system can be inserted at ~~**that**~~ **the** time **of removal, provided pregnancy has been excluded.**

~~**The woman should be advised how to check the threads of Mirena.**~~

- Section 4.6

The existing warning should be amended as follows:

The use of [brand name] during an existing or suspected pregnancy is contraindicated, see section 4.3 Contraindications. If the woman becomes pregnant when using [brand name] **the system should be removed as soon as possible** ~~**timely removal of the system is strongly recommended**~~, since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labor. Removal of [brand name] or probing of the uterus may **also** result in spontaneous abortion. Ectopic pregnancy should be excluded.

~~**If the intrauterine contraceptive cannot be gently removed, termination of the pregnancy may be considered**~~. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

~~**Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of virilizing effects in the fetus should be taken into consideration. Clinical experience of the outcomes of pregnancies under Mirena is limited due to the high contraceptive efficacy, but the woman should be informed that, to date, there is no evidence of birth defects caused by Mirena use in cases where pregnancy continues to term with Mirena in place.**~~ **In addition, an increased risk of virilising effects in a female foetus because of the intrauterine exposure to levonorgestrel cannot be excluded. There have been isolated cases of masculinisation of the external genitalia of the female foetus following local exposure to levonorgestrel during pregnancy with an LNG-IUS in place.**

Package Leaflet

Section 2

Expulsion

The muscular contractions of the womb during menstruation may sometimes push the IUS out of place or expel it. **This is more likely to occur if you are overweight at the time of IUS insertion or have a history of heavy periods. If the IUS is out of place, it may not work as intended and therefore, the risk of pregnancy is increased. If the IUS is expelled, you are not protected against pregnancy anymore.**

Possible symptoms **of an expulsion** are pain and abnormal bleeding **but [brand name] may also come out without you noticing.** ~~**If the IUS is displaced, the effectiveness may be reduced. If the IUS is expelled, you are not protected against pregnancy anymore. It is recommended that you check for the threads with your finger, for example while having a shower. If you have signs indicative of an expulsion or you cannot feel the threads, you should avoid intercourse or use another contraceptive, and consult your doctor.**~~ As **[brand name]** decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

It is recommended that you check for the threads with your finger, for example while having a shower. See also section 3 "How to use [brand name] – How can I tell whether [brand name] is in place?". If you have signs indicative of an expulsion or you cannot feel the threads, you should ~~**avoid intercourse or**~~ **use another contraceptive (such as condoms), and consult your** ~~**doctor**~~**healthcare professional.**

Pregnancy:

[…]

If you become pregnant with [brand name] in place, you should **see your healthcare professional immediately to** have [brand name] removed**.** ~~**as soon as possible. If you leave Mirena**~~ **The removal may cause a miscarriage.**~~**, h**~~ **However, if [brand name] is left** in place during pregnancy, **not only is** the risk of having a miscarriage **higher, but also the** ~~**infection or**~~ **risk of** preterm labor**.** ~~**will be increased. higher.**~~ **If [brand name] cannot be removed, talk with your healthcare professional about the benefits and risks of continuing the pregnancy. If the pregnancy is continued, you will be closely monitored during your pregnancy and you should contact your doctor right away if you experience stomach cramps, pain in your stomach or fever.**

[Brand name] contains a hormone, called levonorgestrel, and there have been isolated reports of effects on the genitalia of female babies if exposed to levonorgestrel intra-uterine devices while in the womb.

~~**The hormone in [brand name] is released into the womb. This means that the fetus is exposed to a relatively high concentration of hormone locally, although the amount of the hormone received through the blood and placenta is little. The effect of such an amount of hormone on the fetus should be taken into consideration but to date, there is no evidence of birth defects caused by [brand name] use in cases where pregnancy has continued to term with [brand name] in place.**~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	14 March 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 May 2022