4 Part VI: Summary of activities in the risk management plan by product

4.1 Part VI.1 Elements for summary tables in the EPAR

Table 4-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Ectopic Pregnancy
	Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting)
	Drug interaction leading to loss of efficacy
Important potential risks	
	Drug exposure during pregnancy
	Drug exposure via breast milk (infant exposure in nursing mothers)
	Effects in women with impaired liver function
Missing information	None

Table 4-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None

Table 4-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None

Table 4-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Ectopic Pregnancy	Guidance is provided in section 4.4 Special warnings and precautions for use of the SmPC.	None
Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting)	Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use.	None
Drug interaction leading to loss of efficacy	Guidance is provided in section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.	None
Drug exposure during pregnancy	Guidance is provided in the following sections of the SmPC: 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data.	None
Drug exposure via breast milk (infant exposure in nursing mothers)	Guidance is provided in the following sections of the SmPC: 4.6 Fertility, pregnancy and lactation and 5.2 Pharmacokinetic properties.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Effects in women with impaired liver function	Guidance is provided in the following sections of the SmPC: section 4.4 Special warnings and precautions, Section 5.1. Pharmacodynamic properties and 5.2 Pharmacokinetic properties.	None

4.2 Part VI.2 Elements for a Public Summary

4.2.1 Part VI.2.1 Overview of disease epidemiology

Globally, use of modern birth control methods has risen slightly, from 54% in 1990 to 57.4% in 2014. Regionally, the proportion of women aged 15–49 reporting use of a modern contraceptive method has risen minimally or reached a relatively stable level between 2008 and 2014 [WHO, 2016]. Emergency contraception is a birth control method that women can use after unprotected sexual intercourse [ESC, 2016]. Depending on the method used, emergency contraception can reduce the risk of pregnancy from a single act of intercourse by between 75 and 99%. Emergency contraceptives (ECs) were introduced in Europe in 2009 and in the United States in 2010 [ICEC, 2016]. Most European Union countries have guidelines on usage of EC [ECEC, 2016]. Hormonal EC use varies according to women's marital status and age. Unmarried women use more hormonal EC than those currently married, as do young women compared to older women [Salazar M, 2014].

4.2.2 Part VI.2.2 Summary of treatment benefits

A study was conducted to compare the effectiveness of levonorgestrel (4470 women) with Yuzpe regimen (3023 women; an age old method of emergency birth control using everyday birth control pills started within 72 hours of unprotected sex). Levonorgestrel was more effective than Yuzpe regimen in routine use, with pregnancy rate of 2.2% in levonorgestrel compared to 3.1% in the Yuzpe group [Leung VWY, 2016].

An analysis was performed in 3 large studies conducted by World Health Organization to investigate whether higher bodyweight and/or body mass index negatively impacts the risk of pregnancy in women receiving levonorgestrel after unprotected sexual intercourse in 5812 women who received levonorgestrel within 72 hours. Levonorgestrel was found to be effective in preventing pregnancy [Gemzell-Danielsson K, 2015].

A study was conducted in 4136 women to compare the efficacy of single dose of levonorgestrel (1.5 mg and 0.75 mg) and mifepristone (10 mg) when administered up to 120 hours after unprotected sexual intercourse, given 12 hours apart. Levonorgestrel 1.5 mg prevented 84% of expected pregnancies compared with 79% when two 0.75 mg tablets were taken 12 hours apart. The use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side-effects [Hertzen HV, 2002].

4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There is no relevant use of {Nationally completed name} for children of prepubertal age in the indication emergency contraception.

4.2.4 Part VI.2.4 Summary of safety concerns

Table 4-5 Important identified risks

Risk	What is known	Preventability
Pregnancy where the baby develops somewhere outside the womb (Ectopic Pregnancy)	A previous ectopic pregnancy or previous infection of the fallopian tubes (pair of tubes along which eggs travel from the ovaries to the uterus) increase the risk of a new ectopic pregnancy. Ectopic pregnancy may continue, even when there is a bleeding from the womb.	The use of levonorgestrel is not advised if patients have a history of ectopic pregnancy or have a history of salpingitis (inflammation of the fallopian tubes). If a patient becomes pregnant after taking levonorgestrel the doctor should check that the pregnancy is not ectopic. This is especially important if the patient develops severe abdominal pain after taking levonorgestrel or if she has previously had an ectopic pregnancy, fallopian tube surgery or pelvic inflammatory disease (an infection of the reproductive organs in women).
Use of medicine in conditions which can affect the effectiveness of levonorgestrel (several disorders in which nutrients are not fully absorbed in the body and vomiting) (Drug use in conditions which can affect the efficacy of levonorgestrel [malabsorption syndrome and vomiting])	Severe malabsorption syndromes such as Crohn's disease (disease causing inflammation of the lining of stomach and gut), might impair the efficacy of levonorgestrel.	The use of levonorgestrel is not advised if patients have a disease of small bowel (such as Crohn’s disease) that inhibits the absorption of the drug. If patients are sick (vomit) within three hours of taking the tablet, they should immediately take another tablet.
Interaction with other medicines which can result in the loss of efficacy of levonorgestrel (Drug interaction leading to loss of efficacy)	Some medicines may prevent levonorgestrel from working properly, these include • Barbiturates and medicines used to treat fits (for example, primidone, phenytoin and carbamazepine). • Medicines used to treat tuberculosis (for example, rifampicin and rifabutin). • A treatment for HIV (Human immunodeficiency virus) infection (ritonavir). • A medicine used to treat fungal infections (griseofulvin).	Patients should consult a doctor or pharmacist before using levonorgestrel if they use any of the mentioned medicines.

Risk	What is known	Preventability
	• Herbal remedies containing St. John's Wort (Hypericum perforatum). • A medicine called ciclosporin (suppresses the immune system). The metabolism (the process by which the body breaks down and converts a medicine into active chemical substances) of levonorgestrel is increased when liver enzyme inducers (medicines that increase the activity of liver enzymes which are naturally occurring chemicals that speed up the rate of a chemical reaction in body) are taken along with it.	

Table 4-6 Important potential risks

Risk	What is known
Drug exposure via breast milk (infant exposure in nursing mothers)	Patients should consult a doctor or pharmacist for advice before taking any medicine if they are breast-feeding. About 0.1% of the maternal dose can be transferred via breast milk to the baby. The active ingredient of this medicine is excreted into breast milk. Therefore, it is suggested that patients should take their tablet immediately after a breast-feeding and avoid nursing at least 8 hours following levonorgestrel administration then drain their milk with a breast pump for 8 hours following tablet taking. In this way patients are taking their tablet well before the next feed and reducing the amount of active ingredient their baby may take in with breast milk.
What could happen in women with liver problems (effects in women with impaired liver function)	Women with liver problems should not take levonorgestrel. Levonorgestrel is processed in the liver, if the liver enzymes are working faster e.g. if there is another drug which speeds up the enzyme activity.

Table 4-7 Missing information

N/A

4.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

4.2.6 Part VI.2.6 Planned post authorization development plan

None

4.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 4-8 Summary of changes to th risk management plan over time

Version	Date	Safety Concerns	Comment
2.0	26 Apr 2016		As per the D68 RMS RO Assessment of Applicant's Response to Day 50 comments (NL/H/2656/001/E/001) received on 03 Mar 2016 for Levonorgestrel 1.5 mg tablet, the following changes were made in the RMP: • RMP was updated in accordance to GVP module V in current EU template and all the relevant sections were updated. • The updated SmPC and PL were included under annex 2. • Annex 3 and 12 were also updated accordingly.
		Important identified risks: Ectopic Pregnancy Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting) Drug interaction leading to loss of efficacy Contraceptive failure **Important potential risks:** Spontaneous abortion Drug exposure during pregnancy	• Safety concerns were updated in line with updated SmPC and PL. •

Version	Date	Safety Concerns	Comment
		Drug exposure via breast milk (infant exposure in nursing mothers) Use beyond 72 hours of unprotected sex **Missing information:** Use in women less than 16 years of age	
2.1	09 Sep 2016	The important identified risk contraceptive failure, the important potential risks spontaneous abortion and use beyond 72 hours of unprotected sex and the missing information use in women less than 16 years of age have been deleted.The important potential risk of effects in women with impaired liver function has been added. The SmPC and PIL have been updated and included.	The safety profile was updated according to PVAR NL/H/2656/001/II/009 dated 09 Aug 2016