RECLASSIFICATION PAPER **MWHEAG/2022/9th Meeting**

1. Type of Application P-GSL RECLASSIFICATION	10. **Number:** [redacted]
2. Proposed Licence Holder [redacted]	11. **Product Name:** [redacted]
3. Manufacturer of Dosage Form [redacted]	12. **Active(s) rINN:** [redacted]
4. Other companies N/A	13. **Therapeutic Classification:** Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives. [redacted]
5. Legal Status Current: Pharmacy (P) Proposed: General Sales List (GSL)	14. **CPSEAG:** No
6. Sale/Supply From retail outlets such as supermarkets, petrol stations and vending machines (without the supervision of a pharmacist) (GSL)	15. **Date of Meeting:** 12 December 2022
7. Risk Management Plan Included Yes	16. **Consideration by other Committees:** [redacted]
8. Indication: [redacted]	17. **Advertising – Prior Vetting Required?** Yes

9. Major Issues/deficiencies:	18. **Assessors:**
Lost opportunity for safeguarding vulnerable people Risk of use [redacted] who are not competent and/or who cannot be safeguarded Risk of misuse of the product due to the numerous and complex messages on the label	[redacted]

Contents

REQUEST FOR CHANGE IN LEGAL CLASSIFICATION FROM P TO GSL OF [redacted] FOR EMERGENCY CONTRACEPTION

EXECUTIVE SUMMARY

This is an application to revise the legal status of [redacted] to allow supply from general sale retail outlets. [redacted] is indicated for [redacted] for the indication: [redacted]

[redacted] is currently available as a Pharmacy (P) medicine in the UK, which means that it can be supplied only from pharmacies and under the supervision of a pharmacist.

If approved as a general sales (GSL) medicine, [redacted] could be supplied from retail outlets such as petrol stations, off licences, newsagents and supermarkets, where there is no medical supervision. Also, if approved, this would be the first oral contraceptive medicine – either regular or emergency - to be available in the UK as a general sales medicine.

Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist. The term “with reasonable safety” has been defined as: “where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

The MAH considers that the importance of accessing emergency hormonal contraception as soon as possible following unprotected sexual intercourse (UPSI) to maximise the effectiveness of it, thereby reducing the number of unwanted pregnancies. Whilst the GSL availability of [redacted] would significantly improve access to the medicine, there is insufficient evidence to support the claim that this would result in a reduction in the number of pregnancies. The suitability of [redacted] as a GSL medicine depends on the ability to adequately manage all risks associated with the medicine on the label. There is a risk that if the medicine is taken without reading the information on the label, or if the information is not followed carefully, [redacted] may not be effective.

Following the assessment of this application, it is not considered possible for the label to replace the role of the pharmacist in the supply of [redacted].

The role of the pharmacist in the supply of [redacted] is extensive. Pharmacists play a crucial role in ensuring [redacted] is only supplied if suitable and the appropriate advice is provided to increase the chance of the medicine being effective, e.g. advice related to the window of use, the action to take if vomiting is experienced, interaction with other medicines, signposting to more effective emergency contraception.

The biggest issue associated with this reclassification is the lost opportunity to safeguard vulnerable women. [redacted] Pharmacists are trained to identify and help manage safeguarding concerns, which can include referral to appropriate services, sharing information with GPs when appropriate and parenteral intervention for children.

[redacted]

There is a considerable risk that as a GSL medicine, individuals may self-select the medicine and take the tablet promptly without reading the label in detail. This is because most women requesting EHC are likely to be aware that the tablet needs to be taken as soon as possible. [redacted] mentioned that it is likely that after taking the pill, the medicine box may be discarded. For [redacted] this is a particular concern, as the medicine box includes important advice and warnings to be aware of after taking the medicine.

[redacted]

This application will be considered by the Medicines for Women's Health Expert Advisory Group (MWHEAG) at its meeting on 12 December 2022, and a summary of the minutes will be presented to the Commission at the meeting on 15 December 2022.

Overall it is considered that [redacted] does not meet the GSL criterion, and therefore this medicine is not considered suitable as a GSL medicine.

Advice is sought from the Commission to confirm whether they agree that [redacted] should not be reclassified from a pharmacy medicine to a general sales list medicine.

1. ISSUE

This is an application to revise the legal status of [redacted] to allow supply from general sale retail outlets.

[redacted] is currently available as a Pharmacy (P) medicine in the UK, which means that it can be supplied only from pharmacies and under the supervision of a pharmacist. The supply of [redacted] from pharmacies usually involves a consultation between the pharmacist and the woman where questions would be asked to determine whether [redacted] is suitable to take.

Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist. The term “with reasonable safety” has been defined as: “where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

If approved as a general sales list (GSL) medicine, [redacted] could be supplied from retail outlets such as petrol stations, off licences, newsagents and supermarkets, where there is no medical supervision.

This increased access also means that [redacted] could be bought from retail outlets by [redacted] including buying the medicine on behalf of another person. [redacted]

As a GSL medicine, the medicine box would be the only source of information available to a woman to determine whether the medicine is suitable for them to take, as prior to sale, they would be unable to view the patient information leaflet.. The label would therefore need to minimise all risks that are currently assessed by the pharmacist.

Whilst the safety profile of [redacted] is generally acceptable, the unrestricted access as a GSL medicine presents a significant safeguarding concern. There is a lost opportunity to safeguard vulnerable populations [redacted] individuals who are subject to domestic violence and sexual abuse.

There is also a likely risk of misuse associated with the GSL availability of [redacted] As a P medicine, pharmacists can advise on precautions to take after intake of [redacted] such as taking an additional dose if vomiting occurs, or advice on when to check for a pregnancy. There is a risk that in the absence of a pharmacist, women may not be aware of essential information which could affect the effectiveness of the medicine.

If approved, this would be the first oral contraceptive tablet to be available in the UK as a general sales list medicine.

2. INTRODUCTION

An application has been received to revise the legal status of [redacted] from P to GSL for [redacted] for the indication:

[redacted]

[redacted]

[redacted]

[redacted]

No changes are proposed to the conditions of supply for the GSL product compared to the P product. The proposed conditions of supply as a GSL medicine are outlined in section 3.5.

This is the first time an application is being considered for the P-GSL reclassification of [redacted]

[redacted]

2.1 Treatment options

The NICE guideline on emergency contraception[1] outlines the current methods of emergency contraception (EC) in the UK.

- Three methods of emergency contraception are currently available in the UK:
  - The copper intrauterine device (Cu-IUD) — a non-hormonal intrauterine device that comes in various shapes and sizes. Most Cu-IUDs are composed of plastic with copper wire or fitted with copper bands, while some also have a central core of silver to prevent copper fragmentation.
  - Oral ulipristal acetate — a selective progesterone receptor modulator taken as a single-dose 30 mg tablet.
  - Oral levonorgestrel — a progestogen taken as a single-dose 1.5 mg tablet.

The copper intra-uterine device is the most effective method of emergency contraception and is the only method of EC that is effective after ovulation has taken place. It can be used by women of any age. This device can only be inserted and removed by a trained healthcare provider, e.g. from a GP surgery or a sexual health clinic. Furthermore the device can be inserted for EC within 5 days (120 hours) after the first unprotected sexual intercourse (UPSI) in a cycle or within 5 days of the earliest estimated date of ovulation, whichever is later.

Levonorgestrel is classified as a pharmacy medicine for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method in adults and adolescents aged 16 years and above.

Ulipristal acetate is currently classified as a pharmacy medicine for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure in women of child-bearing age.

[1] Contraception – emergency, National Institute for Health and Care Excellence, 2021

3. RECLASSIFICATION FROM PHARMACY (P) TO GENERAL SALES LIST (GSL)

The sale and supply of medicines is controlled by The Human Medicines Regulations 2012. All medicines marketed in the UK are classified according to one of the three following categories:

• Prescription Only Medicines (POM) – available only on a prescription

• Pharmacy (P) – available under the supervision of a pharmacist

• General Sale List (GSL) – available in general retail outlets such as supermarkets and petrol stations

Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist. The term “with reasonable safety” has been defined as: “where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

The MAH’s clinical overview providing justification for GSL legal status is provided in Annex 4.

4. BACKGROUND TO THE APPLICATION

4.1 Licensing History

[redacted]

4.2 Application for GSL status

In May 2022, a reclassification application was submitted for assessment. [redacted]

4.3 MAH rationale for GSL status

The MAH considers that the availability of [redacted] as a GSL medicine would be beneficial as the increased access to the medicine could reduce the rate of unintended pregnancies. There are currently no other GSL emergency hormonal contraceptives, and instead women usually obtain supply of EHC from a pharmacy, on prescription from a GP or from a sexual health clinic.

4.4 Proposed conditions of supply as a GSL medicine

No changes are proposed to the conditions of supply for the GSL medicine compared to the P medicine. Therefore if approved, [redacted] would be supplied under the following conditions:

- Indication: [redacted]

- For [redacted]
- Strength: [redacted]
- Formulation: Oral tablet
- Dose: [redacted]
- Maximum pack size: 1 tablet

The following table highlights the conditions when [redacted] should not be taken, and conditions which would require a woman to speak to a doctor or pharmacist before purchasing [redacted] for the current P product, and the conditions proposed by the company [redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table 1: A comparison of the contraindications and warnings between the current P and proposed GSL medicine as outlined in the patient information leaflet and label.

4.5 Expert Support and Commissioned Research

A clinical expert statement in support of this application has been provided by [redacted]

Report of Non-Profit Market Research

The MAH commissioned research with various non-profit organisations (NPO) in the UK.

Three organisations consented to participate in this market research. Two of these organisations were classified as national sexual health advisory services/ service providers:

- [redacted]
- [redacted]

The third organisation withheld consent to be named and had this clause removed from their market research agreement. [redacted] are therefore unable to name them but have stated that they were a women's charity dealing with domestic violence.

Overall, [redacted] was strongly supportive of the reclassification, arguing that it is a safe and effective product.

The domestic violence NPO thought that on balance, increased access through reclassification outweighed the risks.

[redacted] expressed concerns regarding the overall benefits. [redacted] was particularly concerned with the potential loss of a wrap-around service, including the offer of quick start contraception and/or IUD and advice about sexually transmitted infections (STIs). They also felt that should reclassification occur, potential consumers must be made aware that they could still access the product for free via other provision routes (i.e., GP surgery or sexual health clinic). However, they indicated that if appropriate information were provided prior to purchase (at the point of sale) these risks could be mitigated.

The full report is provided as Annex 2 to this report.

<u>Report of Pharmacy Organisation Market Research</u>

Three pharmacy organisations were interviewed by a third party to discuss their hypothetical assessments of the benefits and risks of making a hormonal emergency contraceptive available as a GSL medicine. They did not review any data/information from [redacted] relating to the [redacted] application and [redacted] did not speak to them directly.

Two of these organisations were happy to be named for the purposes of the report and were:

- [redacted]
- [redacted]

The third organisation withheld consent to be named and had this clause removed from their market research agreement. [redacted] are therefore unable to name them but have stated that they were a UK community pharmacy organisation.

The pharmacy organisations participating in this research were all opposed to the reclassification of [redacted] from P to GSL, stating that EHC should remain a P medicine due to the value of the current pharmacy consultation.

Overall pharmacy organisations placed high value in the 'wrap-around services' provided by pharmacists during the provision of EHC, including the ability to support informed choice, impart public health advice, signpost to other services and answer questions. In general, they perceived that safeguarding was the greatest risk posed by GSL access of [redacted]

The full report is provided as Annex 3 to this report.

5. SAFETY ASSESSMENT OF SUITABILITY FOR GSL AVAILABILITY

5.1 Efficacy

[redacted]

5.2 Hazard to health

A key aspect of the GSL criterion that must be considered in the reclassification of [redacted] to GSL status is that it does not present a hazard to health without the supervision of a pharmacist.

The following is discussed in detail in this section:

- PSUR[redacted]
- Adverse events
- Signals
- Safety reports in a country with GSL-like provision
- Adverse events – areas of interest
- Breast-feeding
- Use in adolescents
- Effects on menstrual cycle
- Repeat use
- Ovarian cysts
- Liver safety
- Coagulation
- Drug Interactions
- Ability to drive
- [redacted]

General safety

The MAH has provided safety data from clinical trials and [redacted] department from first launch on [redacted] to [redacted].

In total, since first launch, approximately 36.3 million women have taken [redacted] worldwide [redacted]

5.2.1 PSUR[redacted]

During the interval reporting period of the latest PSUR [redacted] 142 serious and 834 non-serious adverse drug reactions (ADRs) were reported from spontaneous sources with an addition of 25 serious adverse events reported from solicited sources.

During the cumulative reporting period, there were 9443 ADRs of which 1631 were assessed as serious originating from spontaneous sources. Additional 640 serious adverse events were received from solicited post-authorisation sources. A total of 5886 Individual Case Safety Reports (ICSRs) were received cumulatively, among them, 1948 were pregnancy reports.

During the interval reporting period, two safety signals were identified and analysed: a [redacted] opened on [redacted] and a [redacted], opened on [redacted]

There were no changes to the Reference Safety Information during the reporting period.

To note, the estimated patient exposure from the International Birth Date (IBD) to 30 April 2021 is approximately 36.3 million (sold packs).

162 pregnancy reports were received during the reporting period of this PSUR.

5.2.2 Adverse events

Safety Data from MAH's database

The safety data from the MAH's database includes the following exposed women: 5481 for clinical development of EC and 36,328,239 women had post-marketing exposure for general safety surveillance.

The MAH has cited three different sources of safety data which have been analysed for this reclassification:

1. Safety data from EC development programme (data from fifteen Phase I pharmacokinetic/pharmacodynamic studies, two Phase II studies, two Phase III studies conducted in the course of the EC clinical development program, and one [redacted]
2. EC post-marketing data reported to [redacted] since launch as a POM [redacted] until [redacted] – total women exposed = approx. 36 million
3. [redacted]

Assessor's comment: The most relevant source of information is the post-marketing data, as [redacted] and there has been considerable exposure to the product (approximately 36 million packs sold). [redacted]

The table below compares the sales data of [redacted] from when it was classified as a POM, compared to when it was classified as a P. Sales data for the UK alone and EEA countries have been provided.

	Total sales		
Region	**Rx launch to P launch**	**P launch to 30 Apr 2021**	**Total cumulative to 30 Apr 2021**
UK	273 151	2 013 599	2 286 750
EEA	1 982 744	16 108 734	18 091 478

Table 2: Patient exposure before (prescription launch to P launch) and after reclassification of [redacted] as a non-prescription medicine in the EEA and the UK (P launch to 30 April 2021)

5.2.2.1 Adverse events reported from clinical development of EC:

Serious adverse events

A total of ten serious adverse events (SAE) have been reported during clinical trials for EC (including Phase I daily dose study):

- bacterial pneumopathy 10 days after intake of [redacted]
- abdominal pain 10 days after treatment with [redacted]
- Grave's disease 4 weeks after the end of daily treatment with [redacted]
- kidney infection after treatment with [redacted]
- pelvic inflammatory disease after treatment with [redacted]
- seizure in an ecstasy user
- pilonidal cyst
- urinary tract infection
- right contact lens related corneal ulcer
- dizziness after treatment with one dose of [redacted]

The MAH has stated that all these SAEs resolved, and all but one (dizziness) were considered by the investigators as not related to the study drug.

In total eight adverse events led to study discontinuation during drug development. The others included a case of hypothyroidism after a single [redacted] vomiting and ovarian cyst rupture after a [redacted], low haemoglobin and two cases of neutropenia after a [redacted] Among these adverse events, only two were considered possibly related to study drug (vomiting and ovarian cyst rupture after [redacted] .

Since the Development International Birth Date (DIBD) [redacted] to [redacted] there have been 51 serious adverse events (SAEs) reported in all interventional clinical studies conducted by [redacted], of which 25 SAEs represented unlisted events.

The MAH has confirmed that there was no Suspected Unexpected Serious Adverse Reaction (SUSAR) reported during the development program of [redacted] for EC.

Altogether, the MAH has stated the SAEs are few in relation to the number of exposed women. There is no signal of any specific organ toxicity in relation to short-term exposure to [redacted]

Assessor's Comments: The MAH has summarised the common adverse events reported during the clinical trials (Phase I-Phase IV) on pages 37-41 of the safety clinical overview. The vast majority of AEs were of mild or moderate intensity and the most frequently reported AEs were headache, fatigue, dysmenorrhoea, abdominal pain and nausea.

5.2.2.2 Adverse reactions reported during post-marketing surveillance

Worldwide data

The MAH has stated that during the cumulative reporting period from launch to [redacted] 5886 ICSRs were received from all sources worldwide, among them, 1948 were pregnancy reports:

• 1334 ICSRs from non-interventional post-marketing studies and other solicited sources encompassing 640 serious ADRs

• 4552 ICSRs from spontaneous sources including literature and competent authorities encompassing 9443 ADRs including 1631 serious ADRs and 7812 non serious ADRs

The common ICSRs are outlined in Table 3 below.

The most frequent ADRs belong to the categories of **reproductive system disorders** (menstruation delayed, vaginal haemorrhage, vaginal discharge, polymenorrhoea, hypomenorrhoea, intermenstrual bleeding, breast symptoms), **gastro-intestinal disorders** (nausea, diarrhoea, abdominal pain, abdominal pain lower/upper, vomiting, abdominal discomfort, abdominal distension), **nervous system disorders** (headache, dizziness), **general disorders** (fatigue) and **musculoskeletal and connective tissue disorders** (back pain).

Number of ICSRs*	5886 ICSRs
Estimated number of women exposed	~ 36.3 million
Gastro-intestinal disorders	
Nausea	403
Diarrhoea	336
Abdominal pain	310
Abdominal pain lower	170
Vomiting	151
Abdominal pain upper	108
Abdominal discomfort	70
Abdominal distension	67
Nervous system	
Headache	207
Dizziness	190
Musculoskeletal and connective tissue disorders	
Back pain	95
General disorders	
Fatigue	179
Reproductive disorders	
Menstruation delayed	790
Vaginal haemorrhage	594
Breast symptoms (pain, tenderness, swelling, discomfort)	263
Vaginal discharge	197
Polymenorrhoea	141
Hypomenorrhoea	121
Intermenstrual bleeding	109
Pregnancy	**1948**

Table 3: Common spontaneous adverse drug reactions reported since launch [redacted]

The MAH considers that the adverse event profile for [redacted] is well characterised as the adverse reactions reported during the development program and post-marketing phase were for the most part mild to moderate in severity.

UK Data

Since [redacted] has been available as a P medicine [redacted] in the UK [redacted], a total of 743 ICSRs (1426 ADRs) were received from all sources in the UK.

The most common ADRs were reported in the following System Organ Class (SOC):

- 368 ADRs (25.8% (368/1426) of the overall ADRs) in the SOC "Reproductive system and breast disorders" including:
    - 215 ADRs relating to menstrual cycle disorders, including 132 ADRs coded with the with the Preferred Term (PT) 'Menstruation delayed', and 19 with PT 'Heavy menstrual bleeding'
    - 68 ADRs coded with the PT 'Vaginal haemorrhage'
- 353 ADRs (24.8% (353/1426)) in the SOC "Pregnancy, puerperium and perinatal conditions" including:
    - 311 ADRs coded with the PT 'Unintended pregnancy'
    - 27 ADRs with the PT 'Abortion spontaneous'
- 181 ADRs (12.7% (181/1426)) in the SOC "General disorders and administration site conditions" coded with the PT 117 Drug ineffective
- 142 ADRs (10% (142/1426)) in the SOC "Gastrointestinal disorders" including:
    - 40 ADRs coded with the PTs 'Abdominal pain', 'Abdominal pain lower' or 'Abdominal pain upper'
    - 39 ADRs coded with the PT 'Nausea'
    - 23 ADRs coded with the PT 'Diarrhoea'
    - 13 ADRs coded with the PT 'Abdominal distension'
    - 7 ADRs coded with the PT 'Vomiting'

Assessor's comment: [redacted] 1426 ADRs have been reported. Compared to the number of sales there has been during this time in the UK (2013599), this number is not considered to be significant. The types of ADRs reported are aligned with the general safety profile of [redacted] which is outlined in the SmPC, e.g. the reproductive side effects and the gastrointestinal side effects.

However, out of the 1426 ADRs reported in the UK [redacted], 328 were coded with the term 'unintended pregnancy' and 'abortion spontaneous'. This equates to almost 1 in 4 ADRs (23%) reported being an unintended pregnancy. There may be a number of reasons for the cases of unintended pregnancy, e.g. if the medicine was not effective, or if a woman was already pregnant and took [redacted] However, this emphasises the need for a pharmacist in the supply of [redacted] to ensure that key messages are not missed, e.g. the window of time to take the medicine, appropriate signposting if [redacted] is not a suitable option etc.

The MAH has provided the number of cases (Table 4) reported for each of the key safety concerns for [redacted] before and after reclassification to a pharmacy medicine. These cases are based on cumulative safety reports from the integrated safety database [redacted] They have concluded that for all safety concerns except bleeding in non-

pregnancy and effects of the interaction with progestin-containing contraception, the numbers of reported cases before and after reclassification in the UK and the EEA represent 0.001% or less of exposed women. Even for bleeding in non-pregnancy and effects of the interaction with progestin-containing contraception, the most frequently reported safety concerns, the numbers of reported cases represent a very small proportion of exposed women; less than 0.004% in the UK and the EEA before reclassification and less than 0.005% after reclassification.

The MAH considers that the data indicates that removing medical supervision has not increased the risk of adverse drug reactions associated with key safety concerns.

		Number of cases pre-switch		Number of cases post-switch	
		UK n (number of pregnancies reported)	EEA n (number of pregnancies reported)	UK n (number of pregnancies reported)	EEA n (number of pregnancies reported)
Liver effects		0	2	2	4
Effects on pregnancy maintenance / Off label use)		0 (0)	2 (0)	3 (0)	7 (0)
Risk of incomplete abortion and heavy bleeding	**Incomplete abortion**	1	5	3	12
	Bleeding in pregnancy cases	3	15	24	82
	Bleeding in non-pregnancy cases	5	73	95	652
Risk of ectopic pregnancy		3	10	17	50
Effects on foetus and newborns		1	6	1	23
Delayed menstrual period>60 days / amenorrhea		0	3	4	16
Ovarian cysts		0	1	1	8
Effects of concomitant use of cytochrome P450 3A4 (CYP3A4) inducers		0 (0)	1 (0)	2 (1)	6 (1)
Effects in patients with severe asthma treated by oral glucocorticoid		0	0	0	1
Effects in women with impaired liver function*		0	0	0	3
Effects of the interaction with progestin-containing contraception*		8 (5)	36 (12)	31 (14)	442 (36)

*The method used to calculate these cases is not the same as that used to calculate similar risks for the BRASS analysis.

Table 4: Number of cases reported for each safety concern in the UK and the EEA for the periods from prescription launch to reclassification as a P medicine and from launch as a P medicine [redacted]

The MAH has stated that the increase in ectopic pregnancies reported and cases of non-bleeding is likely due to the increased usage from POM-P. The MAH considers that the move to P status also allowed the brand to directly engage with the general public via websites and social media, greatly expanding knowledge about the product and providing a much improved opportunity to collect direct feedback on user experiences via 'safe and familiar' consumer-friendly technology platforms.

The MAH also considers that as doctors are familiar with contraception, a woman presenting with non-pregnancy bleeding is unlikely to be considered as a side effect of [redacted] and is therefore unlikely to report this as a side effect for a POM. However for a P medicine, a woman would be concerned of ectopic pregnancy symptoms or unexpected bleeding and is therefore more likely to report it.

Overall, the MAH considers that the increased product usage, the change of primary reporter and the greater opportunity to identify reports has led to an increased in reports for ectopic pregnancy and non-pregnancy bleeding.

Assessor's comment: It is agreed that the increased access to the medicine from POM-P is likely to result in an increased usage of [redacted] and therefore an increased reporting rate of side effects.

The reclassification of [redacted] is likely to further increase the product usage and hence the reporting rate of side effects. This emphasises the need for women to be aware of the symptoms which would require urgent medical advice to be sought, which is particularly important for first-time users who may not be aware of the symptoms which need to be reported.

5.2.3 Signals

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2.4 Safety reports in a country with GSL-like provision

The MAH has provided safety data from Norway, as the supply of non-prescription medicines in a pharmacy in Norway does not require the supervision of a pharmacist. Consumers are able to self-select and purchase medicines from the pharmacy shelf which is similar to a GSL supply model.

Post-marketing safety data from Norway for the period following reclassification were analysed and compared with the post-marketing safety data for the period following reclassification of [redacted] as a pharmacy medicine in the UK and in the EEA as a whole. Between POM launch and P launch there were [redacted] in Norway and after P launch there were 439,891 sales.

Safety concern		Number of cases post-switch		
		Norway	UK	EEA
		n (number of pregnancies reported)	n (number of pregnancies reported)	n (number of pregnancies reported)
Liver effects		0	2	4
Effects on pregnancy maintenance / Off label use		0 (0)	3 (0)	7 (0)
Risk of incomplete abortion and heavy bleeding	Incomplete abortion	0	3	12
	Bleeding in pregnancy cases	3	24	82
	Bleeding in non-pregnancy cases	13	95	652
Risk of ectopic pregnancy		4	17	50
Effects on foetus and newborns		1	1	23
Delayed menstrual period>60 days / amenorrhea		1	4	16
Ovarian cysts		0	1	8
Effects of concomitant use of CYP3A4 inducers*		0 (0)	2 (1)	6 (1)
Effects in patients with severe asthma treated by oral glucocorticoid		0	0	1
Effects in women with impaired liver function*		0	0	3
Effects of the interaction with progestin-containing contraception		7 (2)	31 (14)	422 (36)

* Number of cases with a medical history in the SMQ 'Hepatic disorders' (not necessarily severe). The method used to calculate these cases is not the same as that used to calculate similar risks for the BRASS analysis.

Table 5: Number of cases reported for each safety concern in the UK, Norway and the EEA for the periods from prescription launch to reclassification to a pharmacy medicine, and from launch as a pharmacy medicine to [redacted]

In Norway, as with the UK and EEA, the number of reported cases for all safety concerns following reclassification represents a very small proportion of exposed patients. The MAH has stated that these proportions are similar to those for the UK and the EEA, indicating that supply of [redacted] in a situation similar to GSL supply, with no pharmacist supervision, is not associated with any increased risk in relation to the key safety concerns.

Assessor's Comments: The safety concerns reported in Norway, where pharmacy medicines are supplied in a similar way to GSL medicines in the UK, demonstrate no safety concerns following reclassification to a P medicine. Compared to the number of sales during this time period (439,891), the number of reported cases for each of the listed safety concerns is low. However, the supply of [redacted] in Norway does not entirely reflect the GSL supply of medicines in the UK, [redacted] Therefore whilst this data is useful, the target population for [redacted] as a GSL medicine in the UK would be [redacted] therefore the supply models are not wholly comparable.

5.2.5 Adverse events

5.2.5.1 Pregnancy

The MAH has considered the possible effects of intake of [redacted] on pregnancy. These effects fall into three categories:

1. The effect on the outcome of pregnancy
2. Pregnancy complication (e.g. ectopic pregnancy, heavy bleeding in case of miscarriage)
3. The effect on the foetus or the newborn

1. The effect on the outcome of pregnancy

Post-marketing data

From post-marketing surveillance since launch in [redacted] a total of 1,948 pregnancy reports after [redacted] use have been received from post-marketing sources. Of these:

- 572 were classed as proven lack of efficacy reports
- 200 were already pregnant when they took [redacted]
- 5 were a potential lack of efficacy **and** inadvertent exposure during pregnancy (due to several intakes)
- 1171 reports had an unknown pregnancy at the time of [redacted] intake

Among the 1948 pregnancies collected in post-marketing setting, 1013 pregnancies have a known outcome (52.0%).

In total there were 2051 pregnancies reported during development of [redacted] for EC (103) and since launch (1948). Of these pregnancies, outcome information is available for 1100. Of these, 285 were carried to term, whereas 595 pregnancies were terminated by elective abortion. Among the remaining pregnancies, 154 ended in spontaneous miscarriage (14.0% of pregnancies with known outcome). This percentage is in line with the 15-20% spontaneous miscarriage rate which is usually reported for the general population.

The MAH has stated that there is no signal of specific adverse reactions in women exposed to [redacted] during pregnancy. There is no signal of a fetotoxic effect of [redacted], and, among delivered babies, there has been no report of defect assessed as related to [redacted] intake.

The MAH has also stated that the exposure of a pregnancy to [redacted] during the cycle of conception does not appear to increase the risk of ectopic pregnancies compared to that of the general population of unexposed pregnancies.

The MAH was requested to specify how many pregnancies reported out of the 1948 pregnancy reports were from the UK since this product has been a P. In total, there have been 328 pregnancies reported in the UK following [redacted] intake since this medicine has been a P in the UK [redacted] These pregnancy reports have been summarised in Table 6 below.

Pregnancy outcome	Number of post-marketing pregnancy cases					
	Total	Timing of exposure				
		Before conception	1st trimester	Potential failure with lack of information excluding an ongoing pregnancy started prior to [redacted] intake	Potential failure with available information about pregnancy age estimation	Unclassified
Unknown outcome*	**164**	50	19	34	4	57
Ongoing	**20**	1	4	4	1	10
Ectopic pregnancy	**17**	2	2	7	2	4
Spontaneous miscarriage	**28**	8	3	9	1	7
Elective termination	**66**	30	13	10	6	7
Live birth	**33**	15	1	7	3	7
Total	**328**	**106**	**42**	**71**	**17**	**92**

** or lost to follow-up.*

Table 6: Number of pregnancy reports in the UK from [redacted] to [redacted] and their outcomes

Of the 328 pregnancies,:

- 106 were classed as lack of efficacy (LOE) as the woman was not pregnant at the time. Each case of LOE is defined by intake of [redacted] by a woman who was not pregnant at time of intake but experienced pregnancy despite intake of the tablet. Of these:
    - 15 pregnancies resulted in live birth, including 2 cases with no information about the health status of the newborn
    - 2 patients reporting lack of efficacy presented with an ectopic pregnancy
    - 8 pregnancies ended in spontaneous abortion
    - 30 pregnancies ended in elective abortion
    - 1 pregnancy was ongoing at time of the data lock point
    - 50 pregnancies were lost to follow-up with unknown outcome

- 42 were classed as a proven inadvertent exposure during pregnancy (women were already pregnant). Of these:
    - 1 exposed pregnancy ended with delivery of a healthy newborn
    - 2 patients had an ectopic pregnancy
    - 3 reports of exposed pregnancies ended in spontaneous abortion
    - 13 exposed pregnancies ended in elective abortion
    - 4 pregnancies were ongoing at time of the data lock point
    - 19 cases of pregnancy were lost to follow-up with unknown outcome

- 180 were classed as unintended pregnancies (reports for which the pregnancy status was unknown at the time of [redacted] intake). This represents 54.9% of received pregnancy cases. Of these:

- 71 case reports are cases of potential lack of efficacy with insufficient information excluding a pre-existing ongoing pregnancy at the time of [redacted] intake. These include:
  - 7 pregnancies which ended with delivery of live newborns, including 1 newborn with no information reported about the health status
  - 7 cases where ectopic pregnancy was reported
  - 9 pregnancies which ended in spontaneous abortion
  - 10 pregnancies which ended in elective abortion with no information on foetus
  - 4 pregnancies which were ongoing at time of the data lock point
  - 34 pregnancies which were lost to follow-up

- 17 case reports are cases of potential lack of efficacy with available information about the pregnancy age estimation confirming that the pregnancy started during the intake cycle. These include:
  - 3 pregnancies which ended with delivery of healthy newborns
  - 2 cases where ectopic pregnancy was reported
  - 1 case of spontaneous abortion was reported
  - 6 pregnancies which ended with elective abortion,
  - 1 pregnancy which was ongoing at time of the data lock point
  - 4 pregnancies which were lost to follow-up.

- 92 cases were unclassifiable, i.e., the information was insufficient to allow any relevant assessment or classification. These include:
  - 7 pregnancies which ended in live birth, including 1 case with no information about the health status of the newborn
  - 4 cases where ectopic pregnancy was reported
  - 7 pregnancies which ended in spontaneous abortion
  - 7 pregnancies which ended with elective abortion, including 1 case with foetal defect (foetal growth arrest at 6 weeks), 1 case of anembryonic gestation, 1 case of blighted ovum, 1 case of missed abortion, 3 reports with no information on foetus
  - 10 pregnancies were ongoing at the time of report
  - 57 pregnancies were lost to follow-up with unknown outcome

Between [redacted] there have been 44 pregnancy reports after [redacted] use.

- 8 were classed as lack of efficacy as the woman was not pregnant at the time.
- 2 were classed as a proven inadvertent exposure during pregnancy (women were already pregnant).
- 34 were classed as unintended pregnancies (reports for which the pregnancy status was unknown at the time of [redacted] intake). Of these,:
  - 13 case reports are cases of potential LOE with insufficient information excluding a pre-existing ongoing pregnancy at the time of [redacted] intake
  - 2 case reports are cases of potential LOE with available information about the pregnancy age estimation confirming that the pregnancy started during the intake cycle.
  - 19 cases were unclassifiable, i.e., the information was insufficient to allow any relevant assessment or classification.

The outcome of all the 372 pregnancy reports received after use of [redacted] in the UK since [redacted] until [redacted] are outlined in Table 7 below.

Pregnancy outcome	Number of post-marketing pregnancy cases					
	Total	Timing of exposure				
		Before conception	1st trimester	Potential failure with lack of information excluding an ongoing pregnancy started prior to [redacted] intake	Potential failure with available information about pregnancy age estimation	Unclassified
Unknown outcome*	**189**	54	21	37	5	72
Ongoing	**20**	4	1	9	1	5
Ectopic pregnancy	**19**	2	2	8	2	5
Spontaneous miscarriage	**30**	8	3	9	1	9
Elective termination	**74**	32	15	11	6	10
Live birth	**40**	16	2	10	4	8
Total	**372**	**116**	**44**	**84**	**19**	**109**

** or lost to follow-up.*

Table 7: Number of pregnancy reports in the UK from [redacted] until [redacted] and their outcomes

Assessor's comment: The efficacy of [redacted] and its effectiveness in preventing a pregnancy occurring would have been assessed and considered when this medicine was reclassified to a P in [redacted].

The MAH's rationale for this reclassification is that the GSL availability of [redacted] would result in a reduction of unintended pregnancies. However, this rationale may not be relevant as the absence of a healthcare professional may result in the inappropriate use of [redacted] where [redacted] may not be effective.

2. Pregnancy complication

Clinical studies

For the 103 pregnancies which occurred during EC clinical development trials, bleeding was reported as an AE in 4 instances as either 'mild' or 'spotting' 4 to 15 days after treatment (8 pregnancies were then lost to follow-up and 5 went on to have an elective termination of their pregnancy).

Bleeding episodes were also analysed from diary data for the Phase III trials pregnancies: compared to non-pregnant women, pregnant women reported slightly more metrorrhagia episodes (bleeding between periods). Women who had a spontaneous miscarriage reported metrorrhagia in 3 cases (from 2 studies). Only one heavy bleeding episode was reported in a woman who had a miscarriage. When metrorrhagia was reported, it lasted a mean of 2 days and occurred a mean of 10 and 15 days after treatment in subjects who then had a

miscarriage. All miscarriages reported in the trials resolved spontaneously without further complication and none required an additional curettage.

The AE profile associated with pregnancy was analysed. All AEs reported corresponded to usual pregnancy-associated symptoms (nausea, vomiting, breast tenderness, abdominal and uterine pain, back pain) or headaches. All reported AEs were qualified as mild or moderate in intensity except in 3 instances where the AE was reported as severe: one case of abdominal cramps 17 days after treatment and 5 days before a spontaneous miscarriage, one case of fatigue 23 days after treatment, and one case of abdominal pain 10 days after treatment.

Post-marketing data:

Since launch, from the 1948 pregnancies reported, 137 pregnancies which ended with a spontaneous abortion, including 2 incomplete spontaneous abortions (tissue left behind in the uterus), were reported, 7 missed abortions (miscarriage without symptoms) and 9 blighted ovum were also reported.

Regarding the risk of incomplete abortion and heavy bleeding, 13.5% of the pregnancies reported with a known outcome ended in a spontaneous abortion (137 out of 1013 pregnancies) in the post-marketing setting. This rate (13.5%) is in line with the rate of spontaneous abortion observed in general population. Spontaneous abortion affects up to 20% of recognised pregnancies.

There were 148 cases of bleeding that occurred in pregnant patients: 93 patients experienced bleeding as signs of spontaneous abortion or missed abortion or blighted ovum or ectopic pregnancy, including 35 reported heavy bleeding, 26 patients experienced bleeding during pregnancy, and 29 patients experienced vaginal bleeding after an induced abortion, including 4 reported heavy bleeding. None of the patients required blood transfusion.

Assessor's Comments: The results from the clinical studies and post-marketing data do not demonstrate any significant pregnancy complications following intake of [redacted] The adverse events reported from pregnant women who had been exposed to [redacted] do not deviate significantly from the expected symptoms experienced during pregnancy. Therefore data from the clinical studies demonstrates that exposure to [redacted] during pregnancy is unlikely to result in harmful complications.

3. The effect on the foetus or newborn

Clinical studies

During development, six healthy babies were delivered.

The seventh was the case of a pregnant woman from a study who delivered a baby subsequently diagnosed with congenital severely altered vision. An independent Data Safety Monitoring Board reviewed the case and confirmed that optic nerve atrophy is a well-known neonatal syndrome and a leading cause of infant blindness in many countries for which only two risk factors have been identified, the young age and primiparity of the mother. The board concluded that the link between this neonatal outcome and [redacted] was unlikely.

Assessor's Comments: The results from the clinical studies have demonstrated that it is unlikely that exposure to [redacted] during pregnancy would have a harmful effect on the foetus/newborn.

Post-marketing data

A total of 21 cases with congenital disorders or 17 effects on foetus and newborn have been collected from the total 2051 pregnancies reported from clinical studies and post-marketing data.

Out of the 21 cases of congenital disorders/malformations, 4 cases led to a termination of pregnancy due to foetal anomaly and 17 cases of live births with congenital anomalies.

Out of the 17 cases of other effects on foetus and newborns, 4 cases led to a termination of pregnancy due to foetal anomaly, and 13 live births have been reported. No case of congenital disorders/malformations and other effects on foetus and newborns was assessed related to [redacted] treatment.

The 21 cases of congenital disorders/malformations represent 1.1% (21/1948) of all pregnancies reported with [redacted] and 2.1% (21/1013) of the pregnancies reported with a known outcome collected in the post-marketing setting. The live birth prevalence of congenital malformations represents 1.7% (17/1013) of the pregnancies with known outcome and 0.9% (17/1948) of the overall pregnancies reported to [redacted] as [redacted] failures or inadvertent [redacted] exposures. The MAH has stated that with regards to incidence/prevalence, congenital anomalies are reported in some 2.5% of live births, with the most common anomalies being cardiac malformations (72/10,000 births), uro-genital malformations (47/10,000 births), abnormalities of the limb (35/10,000) and orofacial clefts (12/10,000 births).

The MAH has stated that the pharmacovigilance database indicates that there is no signal of a fetotoxic effect of [redacted] the observed anomalies having not been assessed as related to the drug.

The MAH has reviewed post-marketing data since [redacted] has been a P in the UK using the Strandardised MeDRA queries (SMQs) ‘Congenital, familial, and genetic disorders (broad+narrow)’, ‘Foetal disorders (broad+narrow)’, ‘Neonatal disorders (broad+narrow)’, the PT ‘foetal exposure during pregnancy’, the PT ‘maternal exposure during pregnancy’ and the age group ‘Neonate’ or ‘Foetus’. A total of one case which resulted in effects on the foetus was retrieved:

A retrospective case of foetal growth restriction was received from a consumer via the [redacted] after her mother experienced unintended pregnancy following [redacted] intake. The 42-year old mother had no reported medical history. Her concomitant medication included amoxicillin, 3 dosage forms daily for a 7 day course, as antibiotic therapy (no further details). On an unspecified date, when the mother was meant to be 9 weeks and 5 days pregnant, it was reported that a scan revealed that the foetus was in a correct position but stopped growing at 6 weeks (no further details). The mother therefore underwent a therapeutic abortion as advised by her physician. Of note, the mother did not take alcohol or drug and she did not smoke while she was pregnant. No further information could be obtained after unsuccessful follow-up attempts. The case was considered as lost to follow-up. The MAH has stated that the information provided does not permit a proper assessment of the causal relationship between [redacted] intake by the 42 year old mother and the foetal growth arrest in this context of maternal exposure during pregnancy. Of note, the cardiac activity status was not specified at the time of the early scan.

The same search was performed since [redacted] has been available as a P medicine in the UK and until 14 May 2022 and 2 additional cases which resulted in effects on the foetus were retrieved:

One prospective serious unlisted case of ankyloglossia congenital, associated with a non-serious unlisted umbilical hernia, was received from a consumer in the UK involving a neonate who was exposed to [redacted] in utero. The baby's mother with no reported medical history and no reported concomitant medication became pregnant in the cycle of [redacted] intake (a lack of [redacted] efficacy could not be ruled out). On 12 June 2021, at 38 weeks of gestation, the mother gave birth to a 2.83 kg baby boy. The baby was born with an umbilical hernia and tongue tied, but he was healthy. On 2 December 2021, it was reported that the hernia had healed itself (on an unspecified date, between October and December 2021) and the tongue tie was stable. At the time of reporting, the umbilical hernia was considered as resolved and the tongue tie was still ongoing. No other information was provided.

The MAH has stated that ankyloglossia is a relatively common congenital oral anomaly with prevalence ranging between 4 and 10 % in newborns. The consequences of ankyloglossia are generally mild, and sometimes include difficulties initiating breastfeeding and poor weight gain. The lingual frenulum typically becomes less prominent as a result of the child's growth and development and the condition often resolves on its own. The cause of ankyloglossia is generally unknown, but there may be a genetic predisposition to ankyloglossia, family history or maternal cocaine use.

The MAH has also stated that umbilical hernia is also a very common health condition, occurring in 10 to 20 % of all children. The condition requires no intervention or investigation in non-complicated cases, and more than 90% will have closed by 2 years of age. Neonatal umbilical hernia is common in preterm infants with low birth weights, Down syndrome, and in conditions with increased intra-abdominal pressure, such as ascites, or congenial hypothyroidism.

The MAH considers that due to the lack of relevant information regarding the mother's relevant medical history (including genetic conditions and family history) and the baby's relevant medical conditions since birth, no medical conclusion can be drawn on a causal role of [redacted] in the occurrence of the events. There was one other case of ankyloglossia in a newborn exposed to [redacted] in utero in the global pharmacovigilance database, and no other case of umbilical hernia.

One retrospective non-serious unlisted case of nystagmus was received from a consumer in the UK involving a baby who was exposed to [redacted] in utero. The mother was a female patient of unspecified age, with no reported medical history or concomitant medication. The mother's last menstrual period was not reported. On an unspecified date, the mother took [redacted] for emergency contraception. Unspecified time after [redacted] intake, the mother found out about her pregnancy, and she reported that she conceived 19 days before the [redacted] intake. During the pregnancy, the mother had hyperemesis gravidarum and symphysis pubis dysfunction. At 37 weeks and 5 days of gestation, the mother gave birth to a healthy male baby, but she experienced placenta previa which required blood transfusions and 'made the delivery extremely difficult' (as reported). Unspecified time after the birth, the baby presented with nystagmus which improved over time. At the time of reporting, the nystagmus was resolving. No other information was provided.

The MAH considers that based on the limited available information available, a causal role of [redacted] in the occurrence of the event cannot be assessed. Concerning the pregnancy, despite the lack of relevant information (such as date of [redacted] ntake and date of delivery), given that the patient conceived 19 days before the [redacted] intake, a causal role of [redacted] cannot be assessed as the patient was already pregnant at the time of [redacted] intake. Regarding the placenta praevia, based on the limited available information (which does not include patient's age or relevant medical history of previous pregnancy or scars on the

uterus from previous surgery or disease, or smoking, alcohol or other drug use during pregnancy), the [redacted] causality cannot be assessed.

The MAH has stated that in systematic reviews, the pooled prevalence of placenta praevia is approximately 1 per 250 births but varies worldwide, and the exact cause of placenta praevia is unknown.

Assessor's comment: The post-marketing data demonstrates that [redacted] does not have a detrimental effect on the foetus or newborn. The reported congenital disorders/malformations are aligned with the normal reporting rates in the general population.

During the period of [redacted] there was only one case retrieved from the company's PV database regarding the number of pregnancies which resulted in detrimental effects to the foetus or newborn.

Considering the number of sales, this case is not considered to be significant. Furthermore, this case does not show a definitive link between the use of [redacted] and the reported issues.

Monitoring of pregnancy cases

The MAH has stated that as pregnancy is a specific area of interest for all medications used for fertility regulation, the originator monitors carefully cases of pregnancy and pursues a special efforts to collect additional information on this topic: a series of additional actions have been agreed with the [redacted] to strengthen the collection of pregnancy cases after [redacted] including the introduction of electronic applications to facilitate case reporting and the possibility for women to report a pregnancy directly. The collection of pregnancy cases with [redacted] is strengthened by the [redacted], where women and Health Care Professionals spontaneously report [redacted] exposed pregnancy cases.

5.2.6 Breastfeeding

A pharmacokinetic study in breastfeeding women has shown that [redacted] is excreted in breast milk up to [redacted]

During post-marketing surveillance, 131 case reports of exposure via breast milk after [redacted] intake were collected; only one of these cases was serious.

From the latest PSUR, there were 14 cases of breastfeeding within a week following [redacted] intake. None of those exposures via breast milk were associated with AEs.

Apart from these rare cases reported in pharmacovigilance, there is little information on human newborns exposed to [redacted] The MAH considers that given the pharmacological profile of [redacted] and in light of the fact that there is no role for progesterone in the newborn infant, it is unlikely to have any detrimental effect on the newborn infant if ingested in breast milk.

Nevertheless, because a [redacted].

The MAH has confirmed that since [redacted] has been a P in the UK, there have been 18 case reports of exposure via breast milk after [redacted] intake. In all of these cases, the mother took [redacted] and breast-fed her child [redacted] and no ADRs related to the exposed babies were reported.

Between [redacted] there were 4 reports of exposure via breast milk. In 3 of these cases, the mother took [redacted] after [redacted] intake. From these, 1 ADR was reported (a 5 week old male baby presented infant colic). In the 4th case, the mother [redacted] ntake and then breast fed her child, but no ADR was reported.

Assessor's comment: The number of cases of exposure to [redacted] via breast milk is not considered to be significant, and of those cases reported, only one presented with an ADR.

5.2.7 Use in adolescents

The MAH has compared the frequencies of AEs and ADRs reported in teenagers <18 years during clinical studies with data from post-marketing sources. Overall, the type and frequency of the most common adverse reactions did not differ significantly between the two comparables.

Post-marketing cases of under 18s exposed to [redacted] showed a slight increase in the reported cases of abdominal pain, dizziness and delayed menstruation. However there were very low numbers reported therefore the MAH considers that this difference is not significant.

The MAH has also compared the incidence and relative risk between under 18s vs over 18s for menstrual cycle effects. There was no statistically significant difference between age classes in terms of incidence, duration and volume of metrorrhagia in treatment cycle from intake of study treatment. Menorrhagia (heavy bleeding) was reported more frequently among subjects aged 18 years or older. A change in length of treatment or post-treatment cycle of more than 7 days was more often reported in younger subjects. Finally a greater change in the menstrual cycle length was observed in subjects under 18 years.

The MAH has confirmed that no specific signal has been detected in adolescents exposed to [redacted] for EC, and as a consequence, [redacted]

Since [redacted] has been a P in the UK there have been 12 case reports (20 ADRs) reported in adolescents aged between 12-17 (4 serious and 12 non-serious):

The 4 serious cases, encompassing 11 ADRs are outlined below:

- 3 cases of pregnancy in a context of lack of efficacy were reported respectively, in a 16 year old female patient and in two 17 year old female patients. The pregnancy ended with an elective abortion in two cases and with delivery of a healthy newborn in the other case.
- 1 case of pelvic discomfort and menstrual disorder (reported as black period), in a 17 year old female patient, occurring 19 days after the intake of two tablets of [redacted] was reported by the Health Authority.

The 8 non-serious cases, encompassing 9 ADRs are outlined below:

- 2 cases of unintended pregnancy were reported respectively in a 16 year old female patient and in a 14 or 15 year old female patient. The pregnancy ended with an elective abortion in one case and the outcome was unknown in the other case.
- 2 cases were reported in the SOC "Reproductive system and breast disorders": 1 case of pelvic pain in a 16 year old female patient occurring the same day as [redacted] intake and one 1 case of heavy bleeding in a 17 year old female patient occurring one day after [redacted] intake.

- 1 case of abdominal discomfort in a 17 year old female patient occurring one day after [redacted] intake.
- 1 case of malaise in a 17 year old female patient occurring the same day as [redacted] intake.
- 2 cases of medication error were reported respectively in a 17 year old female patient and in a 13 year old female patient: 1 case of expired drug administered and 1 case of wrong technique in product usage where the patient chewed the tablet instead of swallow. No associated ADR was reported in both cases.

Between [redacted] there were 2 case reports reported (both were non serious):

- 1 case of diarrhoea in a 17 year old female patient occurring the same day as [redacted] intake.
- 1 case of heavy bleeding in a 17 year old female patient occurring two days after [redacted] intake.

Assessor's comment: [redacted] The numbers and the types of adverse events reported since [redacted] are not considered to be significant. Therefore the data provided by the MAH confirms that there has not been an increased risk in AEs in adolescents since this product has been a P in the UK.

[redacted]

5.2.8 Effects on menstrual cycle

The main adverse reactions reported to pharmacovigilance were effects on the menstrual cycle. Cumulative pharmacovigilance cases are as follows on the effect on menstrual cycle: menstruation delayed (790), polymenorrhoea (141), hypomenorrhoea (121), intermenstrual bleeding (109), heavy menstrual bleeding (104), menstrual disorder (64), dysmenorrhoea (48), amenorrhoea (20), menstruation irregular (12), oligomenorrhoea (2). Only ten (10) out of 1,363 of these cases were serious.

The MAH has concluded from clinical studies that use of [redacted] esults in an average two day delay in the onset of the next menstrual period, [redacted] where treatment cycle is usually shortened by approximately 1.5 days. Less than one quarter of women experienced light intermenstrual bleeding, and the volume of menstrual bleeding is similar to what is observed at baseline and after [redacted]

Since [redacted] has been a P in the UK, there have been 191 cases related to the menstrual cycle disorders encompassing 216 ADRs (6 serious and 210 non-serious):

- Menstruation delayed was reported in 132 cases including 1 serious case:
    - This serious report was received from a consumer via the MHRA and involved a 32 year old female patient with no reported medical history or concomitant medication. One day after [redacted] intake for emergency contraception, the patient experienced excessive flatulence, excessive bloating, increased thirst and dry throat. Moreover, at an unknown date (estimated as within 1 month after [redacted] intake by the company, based on

the date of reporting), the patient presented with a delayed menstruation. At the time of reporting, the patient recovered from dry throat and increased thirst respectively after 8 and 9 days and was recovering from excessive flatulence and excessive bloating whereas the outcome of the delayed menstruation was unknown. All these events were assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.

- Heavy menstrual bleeding was reported in 19 cases including 2 serious cases :
    - The first serious report was received from a consumer via the MHRA and involved a 24 year old female patient, with no reported medical history or concomitant medication. One day after [redacted] intake for post coital contraception, the patient presented with loss of appetite, sickness, vomiting, insomnia, heavy period, stomach cramps and headache. At the time of reporting, all the events were ongoing. All these events were assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.
    - The second serious report was received from a pharmacist and involved a female patient of unknown age, with a medical history of asthma treated with an unspecified inhaler. 7 days after [redacted] intake as emergency contraception, the patient experienced prolonged period with brownish bleeding for 2 weeks. She reported that the menstrual flow was normal. At the time of reporting, the event was resolving. No other information was provided. This event was assessed as serious (other medically important condition seriousness criteria) by the pharmacist. No other information was provided.
- Hypomenorrhoea was reported in 16 non-serious cases
- Polymenorrhoea was reported in 14 non-serious cases
- Intermenstrual bleeding was reported in 11 non-serious cases
- Dysmenorrhoea was reported in 9 cases including 1 serious case:
    - This serious report was received from a consumer via the MHRA and involved a 32 year old female patient with no reported medical history or concomitant medication. The same day she took [redacted] for emergency contraception, the patient presented with the following events (as reported): less discharge from vagina, dry vagina, nausea, abdominal (stomach) pain and discomfort, hot flushes, dry throat, feeling thirsty, headache, dizziness, mood swings, vaginal irritation, genital pain, genital itching, loss of concentration, emotional disorders, anxiety, sleepiness, painful periods, pelvic pain, breast tenderness, unusual sensation in eye, back pain, tiredness, diarrhoea, heartburn, wind, dry mouth and lesser sex drive ("actually a complete loss of sex drive"). The day after, she recovered from flatulence, dry mouth, heartburn, diarrhoea, tiredness and back pain. Two days after [redacted] intake, she recovered from breast tenderness, painful periods, pelvic pain and abnormal sensation in the eye. Moreover, she recovered from loss of libido with an unspecified sequelae. On the third day, she recovered from abdominal discomfort, dry throat, nausea, hot flushes, abdominal pain and increased thirst and on the sixth day, she recovered from concentration loss, genital itching, dizziness, emotional disorder, sleepiness, mood swings, headache, genital pain, vaginal irritation and anxiety. At the time of reporting, vaginal discharge abnormality and vaginal dryness were ongoing. All these events were assessed as serious (other medically important condition

seriousness criteria) by the Health Authority. No other information was provided.

- Menstrual disorder was reported in 6 cases including 2 serious cases:
    - The first serious report was received from a consumer via the MHRA and involved a 17 year old female patient, with no reported medical history and concomitant medication which included spermicide with diaphragm. The patient took 2 tablets of [redacted] and 19 days later, she presented with black period and pelvic pressure. At the time of reporting, both events were ongoing. Both events were assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.
    - The second serious case corresponds to the report described above with the preferred term (PT) 'Heavy menstrual bleeding".
- Amenorrhoea was reported in 4 non-serious cases
- Menstruation irregular was reported in 2 non-serious cases
- Oligomenorrhoea was reported in 2 non-serious cases
- Withdrawal bleed was reported in 1 non-serious case

No case with 'Menstrual discomfort', 'Premenstrual pain' or 'Premenstrual syndrome' was reported during this period.

From [redacted] there were 56 cases related to menstrual cycle disorders encompassing 75 ADRs (5 serious and 70 non-serious):

- Menstruation delayed was reported in 37 non-serious cases
- Heavy menstrual bleeding was reported in 6 cases including 3 serious cases:
    - The first serious report was received from a consumer via the MHRA and involved a 26 year-old female patient with no relevant medical history. Her concomitant medication included paracetamol and tranexamic acid, for both unspecified start date, dosage, route of administration and indication. Following [redacted] intake for emergency contraception, the patient did not have any menstrual period for 151 days (coded as 'amenorrhoea') and finally had her menstrual period which lasted 35 days. Hormonal levels and general blood parameters were normal. Sexually transmitted infection (STI) swabs were also negative. Both events were assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.
    - The second serious report was received from a consumer via the MHRA and involved a 30 year old female patient, with no relevant medical history and no reported concomitant medication. Two days after [redacted] intake for emergency contraception, the patient presented with heavy bleeding. She also complained of mild cramping and pelvic pain when sitting down. At the time of reporting, the events were ongoing. The event 'heavy period' was assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.
    - The third serious report was received from a consumer via the MHRA and involved a 48 year old female patient, with no reported medical history or concomitant medication. One day after [redacted] intake for emergency contraception, the patient experienced heavy vaginal bleeding (heavy menstrual bleeding) that lasted for 5 days, as well as painful period (dysmenorrhea), severe night sweats, anxiety and racing heart. At the time of reporting, all events had resolved. All these events were assessed as serious

(other medically important condition seriousness criteria) by the Health Authority. No other information was provided.

- Hypomenorrhoea was reported in 7 non-serious cases
- Polymenorrhoea was reported in 7 non-serious cases
- Dysmenorrhoea was reported in 7 cases including 1 serious case:
    - This serious report corresponds to the report described above with the PT 'Heavy menstrual bleeding".
- Menstrual disorder was reported in 4 non-serious cases
- Amenorrhoea was reported in 4 cases including 1 serious case:
    - This serious report corresponds to the report described above with the PT 'Heavy
      menstrual bleeding".
- Menstruation irregular was reported in 2 non-serious cases
- Premenstrual pain was reported in 1 non-serious case

No additional case with 'Intermenstrual bleeding', 'Menstrual discomfort', 'Oligomenorrhoea', 'Premenstrual syndrome' or 'Withdrawal bleed' was reported during this one-year period.

Assessor's comment: The number and type of ADRs reported related to menstrual cycle effects is aligned with the other worldwide PV data provided by the MAH. It is already established that [redacted] can result in effects to the menstrual cycle, and the data provided by the MAH does not deviate from what is already known.

5.2.9 Repeat use

220 cases of repeated use in the same cycle were reported to pharmacovigilance since launch up to [redacted]

In 117 cases, ADRs were reported:

- With more than one occurrence (more than one ADR was reported in some cases): Menstruation delayed (48), Vaginal haemorrhage (23), Abdominal pain (13), Nausea (11), Diarrhoea (9), Dizziness (7), Back pain (6), Abdominal pain lower (5), Abdominal distension (4), Heavy menstrual bleeding (4), Rash (4), Intermenstrual bleeding (4), Breast tenderness (4), Headache (3), Increased appetite (3), Hypomenorrhoea (3), Breast pain (3), Genital haemorrhage (2), Pelvic pain (2), Menstrual disorder (2), Breast swelling (2), Breast discomfort (2), Vomiting (2), Polymenorrhoea (2), Amenorrhoea (2), Urinary tract infection (2), Somnolence (2).
- In association with pregnancy in 33 cases including: 10 cases of unintended pregnancies and exposure during pregnancy, 10 cases of unintended pregnancies with drug ineffective, 3 cases of exposure during pregnancy.

In 102 cases, there were no ADRs reported.

In the latest PSUR [redacted] a total of thirty-six cases of several [redacted] intakes in the same menstrual cycle were reported. 17 of these were associated with ADRs (similar to the ADRs outlined above), 8 were associated with pregnancy and 11 did not experience any ADR.

The following is an extract from an FAQ from the [redacted] which provides advice on whether the medicine can be taken repeatedly during the same menstrual cycle:

[redacted]

The MAH has stated that the review of the cases of repeated use in the same cycle showed that several intakes of [redacted] in the same cycle is well tolerated with a safety and bleeding profile similar to the one established for a [redacted]

They have also cited a study which shows that repeated administration (every 5 or 7 days for 8 weeks) is safely tolerated. A prospective open-label exploratory study was conducted to obtain additional data on the pharmacodynamic effects of repeated dose of [redacted] during an 8-week period (effects on ovulation inhibition, hormonal levels, endometrium and cervical mucus). Safety and tolerability data of repeated use of [redacted] were also collected. The study demonstrated a similar safety profile to the previously reported single use studies with no new safety concerns identified, as a result of multiple use. The conclusion of the study includes the following: safety data indicate that [redacted] could be safely administered if needed more than once for emergency contraception in a given menstrual cycle. The EMA reviewed the data and concluded that repeat administration of [redacted] n the same cycle was safe.

The MAH consider that several [redacted] intakes in the same cycle is not a medication error and is not a contraindication. They consider that the high number of ADRs are because most women will report 'repeat use in the same cycle' when it is associated with an ADR. Therefore the number of repeat use episodes without an associated adverse event is likely significantly underestimated, causing the number of adverse event reports to appear artificially high.

Assessor's comment: It is agreed that the increased use as a P medicine has resulted in the increased reporting rates of ADRs from women who have repeatedly used [redacted] in the same cycle.

Currently, women requesting to obtain another supply of [redacted] in the same menstrual cycle can receive this from a pharmacy or from a sexual health clinic. As a GSL medicine, it is important that women are aware whether they can take another tablet within the same

cycle, and therefore the MAH have proposed to include a reference to this on the carton label.

5.2.10 Ovarian cysts

The MAH has stated that ovarian cysts were observed at systematic ultrasonographic examination in five clinical studies.

Since launch up to [redacted], 13 cases of cysts or ovarian cysts, including 1 case which was included with the newly added MedDRA PTs, 'polycystic ovaries' and 'cyst removal' for this PSUR, have been reported. In all cases, no medical conclusion could be drawn on [redacted] causal role in the occurrence of the ovarian cyst. During long-term exposure to [redacted] for uterine fibroids, functional ovarian cysts were observed during and after treatment in 1.5% of patients and in most of the cases spontaneously disappeared within a few weeks. In summary, only a few ovarian cysts (likely to be persistent follicles) were found during clinical trials with no clinical consequence.

Assessor's comments: There have been a very low number of ovarian cysts reported since this licence was approved in [redacted]. There does not appear to be a causal link between the use of [redacted] and the occurrence of an ovarian cyst. Therefore the availability of this product as a GSL medicine is not likely to increase the risk of ovarian cysts occurring in women purchasing [redacted]

5.2.11 Liver safety

The MAH has stated that since launch, 6 cases of hepatic disorders were collected, and no signal was observed in post-marketing surveillance of [redacted]

[redacted]

[redacted]

[redacted]

[redacted] No concern has been raised about serious liver injury with [redacted] and there are no changes to its use.

Moreover, following the [redacted]

Assessor's Comments: As specified by PRAC, there are no liver safety concerns for [redacted] and there has been no signal of liver toxicity in relation to this medicine. The availability of this medicine as a GSL medicine is unlikely to increase the risk of liver toxicity.

5.2.12 Coagulation

Based on clinical trials and studies for clinical development, the MAH has stated that there is no signal related to the intake of [redacted] and any modifications in coagulation parameters or any increased risk of thrombotic events.

Assessor's comments: No data has been provided to indicate that there is an existing risk of the effect of [redacted] ntake on the modification of coagulation markers as a P medicine. Therefore, the GSL availability of this medicine is unlikely to affect this risk.

5.2.13 Drug Interactions

The MAH has stated that from the results of 5 clinical studies, concomitant use of [redacted] with erythromycin, ketoconazole, esomeprazole, fexofenadine and rifampicin did not result in specific safety related concerns.

The MAH has also confirmed that since this product has been marketed, there were a total of 76 cases of drug-drug interactions and only one was associated with a serious adverse event.

[redacted]

Since [redacted] has been a P in the UK, there have been 2 cases of concomitant use with CYP3A4 inducers. Both of these cases involved use with St John's wort where 1 was a serious case, and are described below:

- A serious case report was received from a consumer via the MHRA and involved a 39 year old female patient, with no reported medical history. Her concomitant medication included Hypericum perforatum (St John's wort) for an unknown indication. On 5 September 2019, the patient took [redacted] as emergency contraception following a barrier method contraception failure. Within a few hours of taking the medication, the patient became paranoid and hysterical, aggressive and withdrawn and would not speak or engage. She felt "unreal and disconnected from the real world and disturbed" (as reported). At the time of reporting, the outcome of the psychosis was reported as resolving, while the outcome of other events was reported as unknown. All these events were assessed as serious (other medically important condition seriousness criteria) by the Health Authority. No other information was provided.
- A non-serious pregnancy report was received from a consumer via the [redacted] stry and involved a 20 year old female patient, with a medical history of mild anxiety and depression, who took 1 tablet of [redacted] as emergency contraception, 8 hours after an unprotected sexual intercourse. Her concomitant medication included Hypericum perforatum (St John's wort) for mild anxiety and depression, taken irregularly (not daily), during the first trimester of pregnancy. The month after [redacted] intake, a 5 week pregnancy was diagnosed by a home pregnancy test. The pregnancy ended with an elective abortion. Of note, this pregnancy was classified as a potential lack of efficacy with insufficient information excluding pre-existing ongoing pregnancy at the time of [redacted] intake.

Since [redacted] has been marketed as a P in the UK, there have been 32 case reports of concomitant use with regular progestin containing hormonal contraception. 14 of these were pregnancy reports:

- A total of 5 pregnancy cases in which concomitant use of a Progestin-Only Pill (POP) with [redacted] were reported. Among them, 2 cases were associated with a possible or confirmed lack of efficacy of the emergency contraception. 1 of these 2 cases corresponded to a quick start of the hormonal contraception on the day of [redacted] intake. No cases corresponded to the use of [redacted] because pills of an ongoing regular hormonal contraception were missed.
- A total of 9 pregnancy cases in which concomitant use of a Combined Oral Contraceptive Pill (COCP) with [redacted] were reported. Among them, 8 cases were associated with a proven LOE or a potential LOE of [redacted]. 3 of these 8 cases corresponded to the initiation (quick start) of a regular hormonal contraception on the day of [redacted] intake. No cases corresponded to the use of [redacted] because pills of an ongoing regular combined contraception were missed.

[redacted]

Between [redacted] there were 3 cases of concomitant use with a progestin containing contraceptive.

Assessor's comment: The data provided does not indicate a significant number of drug-drug interactions that have been reported since [redacted] has been a P in the UK. According to the [redacted] the algorithm refers any woman who is

taking any medication to the pharmacist who will be able to advise on whether the product is suitable or not. This implies that some level of HCP input is required. As a GSL medicine, it would be imperative for the medicine box to include a list all interacting medicines which would preclude the use of [redacted] However, even if all medicines are included on the medicine box, there is a high risk that some or all of the information may not be read, resulting in inappropriate use of [redacted] and a possible loss of efficacy of the pill.

5.2.14 Ability to drive

The MAH has stated that dizziness was reported in 22 cases, during clinical trials among which 3 were considered as serious. There have been 191 post-marketing cases of dizziness, of which 17 were classed as serious. There were 7 cases of syncope reported spontaneously since launch and none was serious. The MAH considers that these events appear infrequent and unspecific and do not suggest inability to drive machines after exposure to [redacted].

Assessor's comments: Compared to the number of packs which have been sold, the number of cases of dizziness that have been reported is not considered to be significant. Currently, there is no specific information in the pharmacy training guide or on the information on the [redacted] which provides specific advice on driving or experiencing dizziness. Therefore it is unlikely that the availability of this medicine as a GSL medicine will increase this risk.

[redacted]

The MAH has stated that there is no evidence to suggest that availability of [redacted] as a GSL medicine would increase the likelihood of inappropriate use in adolescents under 16.

[redacted]

They have stated that the safety profile observed in women less than 18 years old in clinical studies and post-marketing is shown to be equivalent to the established safety profile in adults.

In the UK, there were 10 reported cases of use in adolescents under 16 years of age among 273 151 uses (0.004%) before reclassification to a P medicine, and 2 reported cases among 1 876 446 uses (0.0001%) following reclassification.

Children under the age of 16 can consent to their own treatment if they are deemed to be competent and to have the ability to fully understand and appreciate what would be involved in taking a course of [redacted] reatment. This is known as being Gillick competent.

Gillick Competency[3]

Gillick competency is often used to help assess whether a child has the maturity to make their own decisions and to understand the implications of those decisions.

Medical professionals need to consider Gillick competency if a young person under the age of 16 wishes to receive treatment without their parents' or carers' consent or, in some cases, knowledge.

If the young person has informed their parents of the treatment they wish to receive but their parents do not agree with their decision, treatment can still proceed if the child has been assessed as Gillick competent.

[3] Gillick competence, NSPCC Learning – August 2022

There is no set of defined questions to assess Gillick competency. Professionals need to consider several things when assessing a child's capacity to consent, including:

- the child's age, maturity and mental capacity
- their understanding of the issue and what it involves - including advantages, disadvantages and potential long-term impact
- their understanding of the risks, implications and consequences that may arise from their decision
- how well they understand any advice or information they have been given
- their understanding of any alternative options, if available
- their ability to explain a rationale around their reasoning and decision making

Fraser Guidelines[4]

Lord Fraser stated that a doctor should always encourage a girl aged under 16 to inform her parents or carers that she is seeking contraceptive advice (or allow the doctor to inform the parents or carers on her behalf). But if she cannot be persuaded to do so they can proceed to give contraceptive advice and treatment as long as certain conditions are met. This includes making sure it's in the girl's best interests for advice to be given and that she understands the advice.

The Fraser guidelines apply specifically to advice and treatment about contraception and sexual health. They may be used by a range of healthcare professionals working with under 16-year-olds, including doctors and nurse practitioners.

Practitioners using the Fraser guidelines should be satisfied of the following:

- the young person cannot be persuaded to inform their parents or carers that they are seeking this advice or treatment (or to allow the practitioner to inform their parents or carers).
- the young person understands the advice being given.
- the young person's physical or mental health or both are likely to suffer unless they receive the advice or treatment.
- it is in the young person's best interests to receive the advice, treatment or both without their parents' or carers' consent.
- the young person is very likely to continue having sex with or without contraceptive treatment.

The MAH have attempted to address each of the Fraser guidelines individually:

(1) the young person cannot be persuaded to inform their parents or carers that they are seeking this advice or treatment (or to allow the practitioner to inform their parents or carers)

[redacted]

[redacted]

[redacted]

(2) the young person understands the advice being given

The MAH has stated that the information provided for [redacted] is clearly set out and describes the use of the product to prevent pregnancy, what to be aware of in the immediate period following use, as well as information pertaining to on-going sexual health and well-being. The MAH believes that the information provided allows young women to make informed decisions as to their immediate and urgent contraceptive need and be fully aware of the implications of this action. [redacted]

(3) the young person's physical or mental health or both are likely to suffer unless they receive the advice or treatment

The MAH has stated that there can be little doubt that an unplanned pregnancy in a young adolescent woman will impact both their physical and mental well-being. Indeed, the emotional trauma of termination would be significant regardless of whether it is spontaneous or clinically induced and continuing the pregnancy to term would be life changing.

(4) it is in the young person's best interests to receive the advice, treatment or both without their parents' or carers' consent

The MAH has stated that by taking proactive and appropriate action to access emergency contraception the young woman is clearly demonstrating her belief that an unplanned pregnancy is not in her own best interest.

(5) the young person is very likely to continue having sex with or without contraceptive treatment

The MAH has stated that the young woman is in need of emergency contraception because she has already had unprotected sexual intercourse, so this proviso no longer applies to the immediate situation.

Child protection concerns

When using Fraser guidelines for issues relating to sexual health, practitioners should always consider any potential child protection concerns:

- Underage sexual activity is a possible indicator of child sexual exploitation and children who have been groomed may not realise they are being abused.
- Sexual activity with a child under 13 should always result in a child protection referral.
- If a young person presents repeatedly about sexually transmitted infections or the termination of pregnancy this may be an indicator of child sexual abuse or exploitation.

Practitioners should always consider any previous concerns that may have been raised about the young person and explore whether there are any factors that may present a risk to their safety and wellbeing.

Practitioners must always share child protection concerns with the relevant agencies, even if a child or young person asks not to.

The reference guide to consent for examination or treatment[5] published by the DoH stipulates that, 'The child's capacity to consent should be assessed carefully in relation to each decision that needs to be made.'

[redacted]

Assessor's comment: There is a significant safeguarding concern related to use of [redacted] in adolescents under 16 as a GSL medicine.

[redacted]

[redacted] However, currently, [redacted] Pharmacists must be reassured that girls under the age of 16 are 'Gillick competent'.

The MAH's justification of the Fraser guidelines being met is not accepted. A healthcare professional would need to check that each of the guidelines have been met, for example, it is not possible for the information on the label to replace a pharmacist and deem whether an adolescent has sufficient maturity and intelligence to understand the implications of the proposed treatment. Furthermore, it cannot be assumed that all adolescents under the age of 16 would be able to comprehend the information on the label. Also, it cannot be assumed that by purchasing [redacted] from a GSL setting implies that an adolescent cannot be persuaded to tell her parents or allow the HCP to tell them. This is a criteria which could only be met after speaking to the adolescent.

Pharmacists are well placed to identify any child protection safety concerns. For example, adolescents aged less than 16 [redacted] may be sexually abused or exploited, and pharmacists may be able to intervene to provide support and appropriately refer.

There is a risk that:

a) [redacted]

b) [redacted]

[5] Reference guide to consent for examination or treatment, Department of Health -2009

5.2.16 Assessor's comments on 'Hazard to health'

The general safety profile of [redacted] is considered to be well-established in a P setting. During the interval reporting period, two safety signals were identified and analysed: a [redacted] opened on 1 July 2020 and a [redacted] opened on 14 April 2021. The [redacted] resulted in an update of the appropriate sections of SmPC and package leaflet. This risk is applicable to other non-prescription medicines which are managed with advice in the product information, and there is not considered to be an increased risk of angioedema in the GSL setting. The [redacted] still remains open and the MAH have proposed to manage this risk in a GSL setting by including symptoms which would require urgent medical advice to be sought.

In the 6 year reporting period, 1426 ADRs have been reported. Compared to the number of sales there has been during this time in the UK (2013599), this number is not considered to be significant. The types of ADRs reported are aligned with the general safety profile of [redacted] Amongst these 1426 ADRs, there have been 328 pregnancies reported in the 6 year reporting period. This equates to almost 1 in 4 ADRs (23%) reported being an unintended pregnancy. There may be a number of reasons for the cases of unintended pregnancy, e.g. if the medicine was not effective, or if a woman was already pregnant and took [redacted] However, this emphasises the need for a pharmacist in the supply of [redacted] to ensure that key messages are not missed, e.g. the window of time to take the medicine, appropriate signposting if [redacted] is not a suitable option etc.

The results from the clinical studies and post-marketing data do not demonstrate any significant pregnancy complications following intake of [redacted] The adverse events reported from pregnant women who had been exposed to [redacted] do not deviate significantly from the expected symptoms experienced during pregnancy. The results from the clinical studies have demonstrated that it is unlikely that exposure to [redacted] during pregnancy would have a harmful effect on the foetus/newborn.

The number and type of ADRs reported related to menstrual cycle effects is aligned with the other worldwide PV data provided by the MAH. It is already established that [redacted] can result in effects to the menstrual cycle, and the data provided by the MAH does not deviate from what is already known.

There have not been a significant number of drug-drug interactions reported in the UK since this medicine has been a P, however this may be because the presence of a pharmacist in the supply of [redacted] has managed this risk, i.e. by ascertaining use of any interacting medicines before supply to determine whether [redacted] would be suitable. This risk is likely to the elevated in a GSL setting, mainly because individuals may take the tablet very promptly without reading all of the interacting medicines on the carton. This in turn could result in [redacted] being ineffective, and possible causing an unintended pregnancy.

To conclude, this aspect of the GSL criterion has not been met, mainly because the absence of a pharmacist could result in important information being missed, such as the signs of an ectopic pregnancy which would require urgent referral, or any medications which could reduce the effectiveness of [redacted]

A significant hazard to health is the use in adolescents under the age of 16. Whilst [redacted]

[redacted]

The ‘hazard to health’ aspect of the GSL criterion has not been met.

5.3 Risk of Misuse

In order to identify the incremental risks, a systematic approach was taken in which the pharmacy training materials and pharmacy checklist for [redacted] were reviewed to identify each instance where it was recommended that a pharmacist should check the customer’s suitability for [redacted] or provide advice to the woman. Each of these instances was identified as a potential incremental risk for a GSL setting with no pharmacist intervention and the evidence for the likelihood of this risk occurring and the clinical consequences should it occur was collated. This evidence and the incremental risks and benefits were reviewed and discussed by a group of independent clinical experts.

The Brass value-tree for GSL [redacted] was validated during a virtual meeting with independent clinical experts. Five clinical experts acted as consultants for the MAH, participating in an independently run group Delphi exercise in which they reviewed the evidence for each of the benefits and risks associated with [redacted] being made available as a GSL medicine as identified in the Brass value tree. This was the only group of experts who reviewed data relating to [redacted] that the MAH included in their submission. These clinical experts all signed consultancy agreements with [redacted] and can be named. They were:

- [redacted]

For each incremental benefit and risk, the panel of five participants reviewed the evidence and was asked to vote individually and anonymously on a 0–3 scale, as to the predicted:

- Likelihood of occurrence; where 0 reflects a behaviour that almost never occurs, 1 means low likelihood, 2 means moderate likelihood and a value of 3 reflects a high likelihood of occurrence
- Clinical impact; where 0 means the event has no clinical impact; 1 means low impact, 2 means moderate impact and 3 means high clinical impact
- For both questions, the panel had the opportunity to select ‘I don’t know’
- The overall attribute score for each benefit was calculated as the product of the attribute’s likelihood of occurrence and clinical impact scores

The results of the poll were then presented to the group and a discussion of the incremental benefit or risk was facilitated to document and understand causes for different judgements (semantic misunderstanding, different types of evidence, different interpretations, or different

values).

If there was high variability in the initial poll results, (defined as variance of ≥2), the poll was then re-conducted, to determine if following discussion, a consensus could be reached

The risks associated with the supply of [redacted] as a GSL medicine are outlined below and summarised in the following sections:

Unintentional misuse

- [redacted]
- Use in pregnancy
- [redacted]
- Use in males
- Accidental use in children (in cases of advance provision)
- Drug interactions
- Use in women with a hypersensitivity to the active or any other excipients
- Use in women with severe hepatic impairment
- [redacted]
- Use in women not required (i.e. as additional 'protection' when one combined oral contraceptive pill is missed)

Intentional Misuse

- Use as primary method of contraception
- Use to interrupt a known pregnancy
- Exceeding a single tablet per UPSI (including taking more than one tablet within 24 hours or over consecutive days)

Worsened outcome due to self-management

- Increased incidence of sexually transmitted diseases (STD), reduced use of condoms
- No 'preventive' services by seeing HCP
- No informed choice of EC options because the customer is not seeing a HCP
- Consumer does not take appropriate actions after using EHC and unintended pregnancy occurs
- Increased unprotected sex
- Lost opportunity for safeguarding (i.e., use in vulnerable/abused women (all ages))

5.3.1 Unintentional Misuse

5.3.1.1 [redacted]
The MAH considers that the GSL availability of [redacted] is unlikely to alter the timespan within which women take the medicine. The MAH has referred to studies cited by [redacted] which indicate that nearly 90% of women present for EHC within the first 24 hours after an episode of UPSI, and the majority of the remainder within 48 hours (well within the indicated timeframe). Presentations after 72 hours are negligible, indicating that women know to seek help within the indicated timeframe, and the likelihood of occurrence is low.

From the latest PSUR, there was only one case of [redacted] intake reported [redacted] which was associated with lower back pain and lower abdominal pain.

The results of a survey conducted by the MAH to assess how often patients make requests that may indicate possible misuse of EHC, including [redacted] and whether and how often

healthcare providers prescribe EHC in ways that may promote misuse showed no incidence of use beyond the labelled [redacted] window. These results suggest a low likelihood of misuse o[redacted], beyond the suggested [redacted] of effectiveness when used in a GSL setting.

The MAH has compared the post-marketing data of [redacted] when it was a POM to that of when it was reclassified to a P. Prior to reclassification as a pharmacy medicine, 5 cases of use [redacted] after UPSI were reported among 273,151 uses of [redacted] (0.002%) were reported in the UK. Following reclassification, there were 4 reported cases among 1 876 446 uses (0.0002%). The MAH considers that this shows no increase in the risk of use [redacted] after UPSI after reclassification as a P medicine, and there is no expectation that the proposed change of supply from P to GSL would change this.

Expert opinion

The likelihood that women would take [redacted] if available as GSL medicine, beyond the suggested [redacted] was estimated to be low to moderate (mean score 1.4), and it was considered that this would have no to a low clinical impact (mean score 0.4). This gave an overall risk attribute score of 0.56.

Proposed mitigation measures

The MAH has stated that in order to mitigate any potential incremental risk related to unintentional misuse[redacted] of UPSI when [redacted] is available as a GSL medicine, a statement will be included on the outer carton outlining the current indication (including the [redacted] and advice that [redacted], should be used as soon as possible following UPSI.

The MAH has included the following statement on the front and back panel of the carton: Take one tablet as soon as possible after unprotected sex or contraceptive failure [redacted]

Assessor's Comments: Women who have previously accessed EHC either through pharmacies may be aware that EHC is to be used as soon as possible after UPSI or contraceptive failure. However, there is a risk that some women, particularly first time users or young adolescents, may not be aware of this and may purchase EHC [redacted] UPSI or contraceptive failure.

In a P setting, pharmacists can determine whether a woman is eligible to take EHC by asking when UPSI or contraceptive failure occurred. There is a risk that in a GSL setting, the public may not be able to calculate [redacted] o determine whether the medicine is suitable for them. Instead, the label could be interpreted broadly as [redacted] which poses a risk of taking the medicine outside of the window of use. [redacted]

Although there is information on the label which informs users about the window of use, the presence of a pharmacist is considered important in emphasising this, and especially to inform women that [redacted] is more effective the earlier it is taken.

5.3.1.2 Use in pregnancy

The MAH has stated that the likelihood of use of [redacted] in pregnancy is low and if it were to occur, would have little clinical impact.

Post marketing pharmacovigilance data (from 30 August 2006 to 2014) from 23 countries reported 282 cases of pregnancies, out of 1.4 million women exposed to [redacted] Findings from the development program of [redacted] have outlined a total of 376 pregnancies in which exposure to [redacted] were reported. While most pregnancies were terminated, all pregnancies that were continued and followed up to delivery ended with live births with healthy outcomes (only one case of optic nerve atrophy, not related to [redacted] was reported). No complications were reported during the course of pregnancy or delivery. Reporting rates of spontaneous miscarriages (13.8%) and ectopic pregnancies (1.1%) in those exposed to [redacted] compared favourably to those from the general population.

[redacted] a [redacted] Since its launch in [redacted] and [redacted] 1948 pregnancies with exposure to [redacted] have been reported [redacted] and these have been followed-up as diligently as possible. Of these pregnancies, outcome information is available for 1082, with pregnancy ending in elective abortion in 532 cases, live birth in 278 cases, spontaneous abortion in 137 cases and in ectopic pregnancy in 66 cases.

The MAH has stated that there is no signal of a fetotoxic effect of [redacted] Regarding the risk of effects on foetus and newborns, out of the 2051 pregnancies (103 in clinical trials plus 1948 post-marketing cases) that have been reported as [redacted] failures or inadvertent exposures to [redacted] a total of 39 cases with congenital disorders or effects on foetus and newborns have been collected.

Prior to reclassification to a P medicine, there were 3 reported cases of use in pregnancy in the UK among 273,151 uses (0.001%), and following reclassification to a P medicine, 37 reported cases among 1 876 446 uses (0.002%).

Expert Opinion

The likelihood of unintentional misuse of [redacted] in pregnancy was considered to be low (mean score 1). Experts agreed that such use is unlikely to have any clinical consequence on the progression of the women's pregnancies. Experts agreed that such use is unlikely to have any clinical consequence on the progression of the women's pregnancies (mean score 0). This resulted in an overall risk attribute score of 0.

Proposed Mitigation measures:

In order to mitigate any potential risk related to unintentional misuse in pregnancy when [redacted] is available as a GSL medicine, a contraindication has been included on the carton label which advises women not to use [redacted] and to speak to a healthcare professional if they are pregnant or if they think they are pregnant. This information is also reflected in the leaflet.

Assessor's comment: It is agreed that use of [redacted] during pregnancy is unlikely to clinically impact the outcome of the pregnancy. The inclusion of pregnancy or a suspected pregnancy as a contraindication on the outer carton is likely to be sufficient to manage this risk.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.1.4 Use in males

This product is only indicated for use in women. In post-marketing pharmacovigilance data from 30 August 2006 to [redacted] there have been two cases of [redacted] use in men. There have been no reported cases of use in males in the UK before or after reclassification to a P medicine.

Expert Opinion:

The experts were unanimous that there was no likelihood of [redacted] being unintentionally misused in males if available as a GSL medicine (mean score 0), an even if it occurred, it would have no or a low clinical impact (mean score 0.2).The total risk attribute score was 0.

Proposed Mitigation measures:

In order to mitigate any risk related to unintentional misuse in men, an on-carton statement is proposed that this medicine is suitable for [redacted] to clarify the intended treatment population. Experts deemed this would be sufficient and agreed that a 'not for use by men' statement on the carton would not be needed.

Assessor's Comments: It is agreed that the risk of use in men is not expected to increase as a result of the GSL availability of this medicine. The target population on the back panel of the outer carton is considered sufficient to manage this risk.

5.3.1.5 Accidental use in children (in cases of advance provision)

The MAH has stated that although the effect of accidental ingestion of EHCs in children is unknown, accidental ingestion of regular oral contraceptive pills rarely causes toxicity in

children, with the most commonly reported adverse effects being transient gastrointestinal discomfort.

Furthermore the MAH considers that there is no evidence on whether such accidents would increase following GSL availability of [redacted] The clinical impact of accidental ingestion in children has not been assessed. However, in post-marketing pharmacovigilance data from 30 August 2006 to [redacted] there have been 3 instances of children being accidentally exposed to [redacted] with no reported ADRs.

In the UK and the EEA, there have been 0 cases of children being accidentally exposed to [redacted] following reclassification as a pharmacy medicine and similarly in Norway, where supply of [redacted] is similar to the UK GSL, there have been 0 cases of children being accidentally exposed to [redacted] from 1 May 2015 to 31 December 2020.

Expert Opinion:
Experts agreed that, for an individual woman, there was no to low likelihood of [redacted] being accidentally used in children (in cases of advance provision) if available as a GSL medicine (mean score 0.6), and that this would have no to a low clinical impact (mean score 0.2).Total risk attribute score 0.12.

Proposed Mitigation measures:
The MAH has stated that in order to mitigate any risk related to unintentional accidental ingestion in children with GSL [redacted] the existing on-carton statement to 'keep out of sight of children' will be replaced by 'keep out of the sight and reach of children' which experts suggested was more usual wording. The currently sealed pack will be retained.

Assessor's Comments: It is unlikely that the GSL availability of [redacted] would increase the risk of accidental use in children. The formulation (tablet) is not similar to a children's medicine (e.g. chewable tablet) and does not contain any flavouring that would encourage use in children. Even if [redacted] was bought in advance and stored at home, it is unlikely that children may take this medicine, and this risk already exists with other GSL medicines which are not indicated for children. In the unlikely event that children did take [redacted] the MAH has stated that only transient GI symptoms are likely to be experienced. No additional warnings on the label to mitigate this risk are considered to be necessary.

5.3.1.6 Drug-drug interactions, which may result in decreased efficacy of EHC or other drug(s)

CYP3A4 inducers/inhibitors

The MAH has stated that there is no evidence to suggest there would be an increase in drug-drug interactions with CYP3A4 inducers/inhibitors if [redacted] were reclassified to GSL status. Drugs or herbal products that induce enzymes, including CYP3A4, such as carbamazepine, phenytoin, rifampicin, St. John's Wort, etc., may decrease the plasma concentrations of [redacted] and its effectiveness. On the other hand, CYP3A4 inhibitors such as itraconazole, ketoconazole, etc., may increase plasma concentrations of [redacted] Concomitant use is therefore not recommended, and additional contraceptive precautions should be taken.

Many commonly used CYP3A4 inducers by women of reproductive age are medicinal products to treat epilepsy. However, the MAH has stated that it is standard practice to prescribe to women of childbearing age newer antiepileptic treatments that do not interfere with CYP3A4 (such as gabapentin, tiagabine, or vigabatrin).

Concomitant use with hormone-based contraception (HBC) or [redacted] *(within the same menstrual cycle)*

The MAH has stated that pharmacodynamic data on the interaction between [redacted] and hormonal oral contraception provide biological plausibility that:

[redacted]

Prior to reclassification to a P medicine, there were 2 reported cases of drug-drug interactions (PT drug interaction or labelled drug-drug interaction error (without clinical consequence)) among 273 151 uses (0.0007%) in the UK, and 0 cases among 1 876 446 uses (0%) following reclassification to a P. The MAH considers that there is no expectation that the proposed change of supply from P to GSL would increase the risk of drug-drug interactions.

Expert Opinion

Experts agreed that, for an individual woman, there was a low to moderate likelihood that drug-drug interactions would increase if [redacted] was available as a GSL medicine (mean score 1.4), and that this would have a low to moderate clinical impact (mean score 1.2). The overall risk attribute score was 1.68.

Proposed mitigation measures:

In order to mitigate any risk related to drug-drug interaction with CYP3A4 inducers/inhibitors, contraindications on the carton have been included which state:

'Do not use [redacted] *and speak to a healthcare professional if:*

- *In the last 4 weeks you have used medicines to treat any of the following: epilepsy, tuberculosis, HIV, fungal infections, or if you have taken herbal remedies containing St John's wort.*
- [redacted]

In order to mitigate any risk related to drug-drug interaction with hormone-based contraception (HBC) or [redacted] a contraindication has been included which states:

'Do not use [redacted] *and speak to a healthcare professional if:*

- *you have taken an* [redacted]

A warning has also been included on the medicine box which states:

[redacted]

The above information is also reflected in the leaflet.

Assessor's comment: The MAH cannot rely on newer anti-epileptics being prescribed to justify the risk of drug-drug interactions. This is particularly important for medicines such as

St John's wort which may reduce the efficacy of [redacted] and is available as a GSL medicine.

There is considered to be an increased risk of drug-drug interactions due to the GSL availability of [redacted]. This is because the current role of the pharmacist includes ascertaining current medication that a woman is taking before [redacted] can be supplied. [redacted] refers women taking any medication to the pharmacist which implies that some level of input from a healthcare professional is required. Unlike other GSL medicines, the consequence of taking [redacted] with a concomitant contraindicated medicine may result in a reduced efficacy and therefore a pregnancy.

The proposed labelling is not considered to be sufficient to manage the risk of drug-drug interactions. If available as a GSL medicine, a full comprehensive list of interacting medicines would need to be included on the carton label. The MAH's proposal, e.g. 'medicines for epilepsy' is not specific and some women, particularly young adolescents, may not be aware of what medication they are taking or what they are for, which could result in [redacted] being taken when unsuitable.

5.3.1.7 Use in women who have hypersensitivity to the active substance or to any of the excipients

The MAH has stated that there is no evidence to suggest that [redacted] as a GSL medicine would increase the use of the product in women hypersensitive to the active substance or excipients of the medicine.

Expert Opinion:
Experts agreed that there was no to a low likelihood that use of [redacted] in women with hypersensitivity to the active substance or excipients would increase if it became available as a GSL medicine (mean score 0.2) because the only way a woman would know that she had a hypersensitivity would be if she had used it previously. As such, the woman is likely to be very careful not to take a product that she had a bad reaction to previously. Although it was not clear what the clinical impact associated with the risk of hypersensitivity would be, it was agreed that the clinical impact would be low (mean score 0.4). The total risk attribute score was 0.08.

Proposed mitigation measures:
The MAH has stated that in order to mitigate any potential risk related to hypersensitivity to the active substance or to any of the excipients, a statement that the product contains lactose and warning about potential allergic reactions to [redacted] and other ingredients has been included on the outer carton.

Assessor's Comments: There is not considered to be an increased risk of use in women who are allergic to [redacted] or any of the other ingredients. The proposed wording on the label is considered adequate to manage this risk.

5.3.1.8 Use in women with severe hepatic impairment

The MAH has stated that [redacted] is not recommended in women with severe hepatic impairment and there is no evidence to suggest that availability of [redacted] as a GSL

medicine would increase the incidence of use in women with severe hepatic impairment. The MAH considers that women with severe hepatic impairment are likely to able to self-identify and therefore recognise the advice to talk to a healthcare professional before using [redacted]

The MAH has cited a study involving 392 women attending family planning clinics in Washington, where all women self-screened correctly with regards to their liver disease or jaundice.

There were no reported cases of use in women with severe hepatic impairment following reclassification to a P in the UK, the EEA or in Norway, indicating that reclassification to a P medicine and availability in a GSL like setting have not increased the risk of unintentional misuse in women with severe hepatic impairment.

Expert Opinion:
The likelihood that use of [redacted] in women with severe hepatic impairment would increase with GSL [redacted] was thought to be none to low (mean score 0.4), and, although it was not clear what the clinical impact would be, it was thought to be negligible (mean score 0). The total risk attribute score was 0.

Proposed mitigation measures:
The MAH has stated that in order to mitigate any potential risk related to unintentional misuse in women with severe hepatic impairment, a contraindication has been included on the outer carton which advises women with severe liver disease not to take the product and to speak to a healthcare professional.

Assessor's comment: It is agreed that women with severe liver disease are likely to be aware of their condition and are also likely to check whether they can take some medicines. The inclusion of a warning on the label is likely to be adequate to manage this risk, and the inclusion of this warning as a contraindication on the outer carton reflects the information in section 4.2 of the SMPC: '*Severe hepatic impairment*: *In the absence of specific studies,* [redacted] *is not recommended.'*

[redacted]

[redacted]

[redacted]

5.3.1.10 Use in women not required [redacted]

The MAH considers that there is no evidence that availability of [redacted] as a GSL medicine would increase the likelihood of use when not required [redacted] However, it is feasible that there might be increased use when not required because of the increased availability of [redacted]

[redacted]

Expert Opinion:
Experts considered that there was a moderate likelihood that use when not required would increase with GSL [redacted] (mean score 1.8), but that the clinical impact would be low (mean score 0.6).

Proposed mitigation measures:
The MAH has stated that in order to mitigate any potential risk of use when not required, the indication has been included clearly on the label which outlines the timeframe of when [redacted] can be taken. The experts noted that this does not specifically state 'don't take this if you've only missed one pill', but as the risk of harm was low, they agreed this was measure was adequate.

Assessor's Comments: It is likely that the increased access to [redacted] may result in women taking the medicine when not required. [redacted]
There is currently no information in the [redacted], or on the [redacted] which state that use after missing one pill would not be required. Therefore, it is likely that [redacted] may have already been supplied on several occasions to women who have missed one pill. The information on the label regarding the indication is considered to be adequate to manage this risk.

5.3.2 Intentional Misuse

5.3.2.2 Use as primary method of contraception

The MAH considers that there is no evidence to suggest that access to [redacted] as a GSL medicine would increase the likelihood of use as a primary contraceptive method. In a web-based survey describing knowledge and use of EHC in 2007 college women in the US, only a minority (4.6%) approved the use of EHC as a replacement for a primary method of birth control.

The UK FSRH guidelines (UK FSRH 2020) state that EHC is intended for occasional use, to reduce the risk of pregnancy after UPSI.

Additionally, the cost of EHC is potentially high, whereas ongoing contraception is freely available from sexual health services and healthcare professionals (HCPs), which would make it even less likely that a consumer chooses to take EHC over regular oral contraception medicines.

Cost

Supply of Emergency Hormonal Contraception (EHC) under a Patient Group Direction in Community Pharmacies:

Patient group directions (PGDs) are written instructions to help a pharmacist supply or administer medicines to patients, usually in planned circumstances. They take a significant amount of time and resource to develop and implement.

Pharmacists can only supply and or administer medicines under PGDs if there is an advantage for the patient without compromising their safety.

Pharmacists can supply EHC for free in line with the requirements of the locally agreed Patient Group Direction (PGD). The PGD will specify the age range of clients that are eligible for the service. Pharmacists will be reimbursed at the lower drug tariff price when dispensing levonorgestrel and ellaOne. The higher drug tariff price will only be reimbursed in exceptional circumstances i.e. if the drug is unavailable from the drug company due to a manufacturing problem.

Pharmacies can provide EHC for free based on the inclusion criteria in the service specification.

Other places where EHC or an IUD can be provided with no charge:

- a GP surgery that provides contraception (some GP surgeries may not provide the IUD)
- a contraception clinic
- a sexual health clinic
- some genitourinary medicine (GUM) clinics
- some young people's clinics
- most pharmacies
- some minor injuries units
- some Accident & Emergency departments

If there is no PGD in place, women can purchase EHC from a pharmacy. Levonorgestrel costs approximately £10 and ellaOne costs approximately £33.

The MAH has stated that even if women do use [redacted] as a regular method of contraception, the clinical consequences are likely to be minimal. They have referenced a

study in 23 women where [redacted] was administered every 5 or 7 days over a period of 8 weeks, ovulation was delayed, and many women experienced irregular bleeding upon ovulation. Assessments of endometrium in these women showed morphological changes associated with progesterone receptor modulator (PRM) exposure. However, women had normal liver function, haematinics blood test and thrombotic markers. [redacted] reviewed the data and concluded that repeat administration of [redacted] in the same cycle was safe.

Expert Opinion:

The likelihood that the use of [redacted] as a primary method of contraception would increase once it becomes available as a GSL medicine was considered to be non-existent to low (mean score 0.8), with a low clinical impact (mean score 0.8). The total risk attribute score was 0.64. However, as one expert noted, frequent UPSI could increase the risk of pregnancy. It was also speculated that the use of [redacted] as a method of contraception may have a small positive clinical impact as using EHC would be preferable to coitus interruptus, using no method of contraception or using spermicide.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk related to intentional misuse in women as a primary method of contraception, the following has been included on the label:

- [redacted] *should not be used as a regular contraceptive method. It is for occasional use only'*.
- '*if you wish to consider alternative contraceptive methods, talk to a healthcare professional to choose one that is suitable for you'.*

Experts advised that the second warning outlined above should be included in the leaflet rather than on the carton, because of a concern that carton would become cluttered and less readable.

Assessor's comment: It is agreed that the risk of using [redacted] as a regular contraceptive is unlikely to increase due to the GSL availability of the medicine. This is mainly due to the cost of EHC, and that there is only one tablet per pack, whereas most women could obtain their regular contraception free via a prescription or free through pharmacies that offer the service with no charge (e.g. via a PGD). However even in the event that [redacted] was taken multiples times in one cycle, the MAH has indicated that the clinical consequences are not likely to be harmful.

The warning related to alternative contraceptive methods that has been included is considered to be unnecessary. The information included on the label should allow a woman to self-select and use the medicine safely, without having to consult the leaflet. Therefore, information related to alternative contraceptive methods should only be included in the leaflet.

5.3.2.3 Use to interrupt a known pregnancy

The MAH has stated that there is no evidence to suggest that availability of [redacted] as a GSL medicine would increase the likelihood of women using EHC to interrupt a known pregnancy.

The MAH has stated that the potential risk of off label use (either use outside the approved time window and/or use in a woman already pregnant) was assessed through a survey

among prescribers in six EU countries. This type of off label use of [redacted] was observed in less than 1% of patients. Notably, the results did not identify any evidence for the use of [redacted] to terminate an established pregnancy.

The [redacted] included data collected from the US [redacted] and from European countries with [redacted] as GSL or over the counter (OTC). There was no evidence for the use of multiple doses (accidental or deliberate) of [redacted] in pregnancy. Similarly, there was no evidence for misuse.

Before reclassification, the UK had 0 reported cases of use to interrupt a known pregnancy among 273,151 uses (0%), and following reclassification, 1 case among 1 876 446 uses (0.00005%). There were 0 reported cases among 422,711 uses (0%) following reclassification in Norway, indicating low rates of use to interrupt a known pregnancy in the pharmacy setting and no increase in rates in a GSL like setting.

Expert Opinion:

The likelihood of increased use of [redacted] to interrupt a known pregnancy when it is available as a GSL medicine was considered non-existent to low (mean score 0.8), with minimal clinical impact (mean score 1). The total risk attribute score was 0.8.

Proposed mitigation measures:

The MAH has stated that in order to mitigate the potential risk related to intentional misuse in women to interrupt a known pregnancy, a contraindication has been included on the label which advises women not to take [redacted] and speak to a healthcare professional if they are already pregnant or think they may be pregnant.

A separate warning has also been included which states [redacted] *does not terminate or interrupt an existing pregnancy'.*

Assessor's Comments: EHC, including [redacted], has been available for many years, and women purchasing it are likely to be familiar with the indication. The low reported numbers of use to interrupt a known pregnancy indicate that this risk is already low. However, the inclusion of [redacted] does not terminate or interrupt an existing pregnancy' could result in women taking [redacted] if they have a known pregnancy, as they think it will not have any effect on the pregnancy. This could undermine the contraindication of use in pregnancy.

5.3.2.4 Exceeding a single tablet per UPSI (including taking more than one tablet within 24 hours or over consecutive days)

The MAH has stated that there is no evidence to suggest that availability of [redacted] as a GSL medicine would increase the likelihood of women exceeding a single tablet dose per UPSI. However, it is conceivable that consumers may take another tablet in the hope that they are increasing the therapeutic effect. However, evidence of use in Norway where supply in pharmacy is without pharmacist supervision, suggests that intentional overdose is unlikely. When asked how frequently they had taken EC in the last 12 months, 10% of women said once; 4% said twice (87% said they had not taken it).

In the event of intentional overdose, no significant safety concern is expected with [redacted] as stated in the currently approved SmPC: "[redacted]

[redacted].'

Data from the "[redacted]" (US and selected European countries including some that have [redacted] as GSL) found there was no signal that any use (accidental or deliberate) of more than one tablet of [redacted] on a single occasion occurred.

In the UK there were 0 cases of intentional overdose among 273 151 uses (0%) before reclassification to a P medicine and 6 reported cases (3 serious) among 1 876 446 uses (0.0003%) following reclassification. These cases are outlined below:

- The first case was a serious pregnancy report which involved a 28 year old female patient, weight 99 kg and height 167 cm, with a medical history of four pregnancies which ended in two live births and in one elective abortion, and a birth defect history in a previous pregnancy (spina bifida, Down's syndrome, bilateral talipes and cleft lip and palate). The patient took 2 tablets of [redacted] 8 hours after unprotected intercourse and became pregnant. At time of [redacted] intake, the patient was not pregnant as determined by an ultrasound scan. The patient had no medical conditions during pregnancy and received no other drugs other than [redacted] and hormonal contraception during pregnancy. One month later, the patient started a regular contraception with Microgynon 30 (ethinylestradiol, levonorgestrel). At 12 weeks and 5 days of gestation, the pregnancy was normal appearing for gestational age, showing a gestational sac with a diameter higher than 20 mm and the presence yolk sac, foetus and cardiac activity. The patient had tobacco intake during the first trimester of pregnancy. She did not have alcohol intake or illicit drug use. Then, this case was considered as lost to follow-up and the outcome of the pregnancy was considered as unknown. Of note, the pregnancy was assessed as compatible with a lack of efficacy of [redacted]
- The second serious pregnancy report involved a 35 year old female patient, with a medical history of fibromyalgia treated with duloxetine, and an obstetrical history of 6 previous pregnancies which ended in 3 lives births, 2 spontaneous abortions and 1 foetal death (no previous history of birth defect nor of elective or therapeutic abortion). The patient took 2 tablets of [redacted] 12 hours after an unprotected intercourse. At time of [redacted] ntake, the patient was not pregnant as confirmed by her last menstrual period date. One month later, an ultrasound scan showed a pregnancy with a gestational age of 5 weeks and 6 days. The intra-uterine pregnancy was of normal appearing for gestational age and the presence of a mean sac diameter more than 20 mm was noted. Few days later, the pregnancy ended with an elective abortion for no medical reason without any complication. The patient had alcohol intake during the first trimester of pregnancy (6-8 units per week), but no tobacco or illicit drug use. Of note, the pregnancy was assessed as compatible with a lack of efficacy of [redacted]
- The third serious case report was received from a consumer via the MHRA and involved a 17 year old female patient, with no reported medical history and concomitant medication which included spermicide with diaphragm, who took 2 tablets of [redacted] as emergency contraception. Nineteen days after [redacted] intake, she presented with black period and pelvic pressure. At the time of reporting, both events were ongoing.

- A non-serious pregnancy report was received from a consumer and involved a 40 year old female patient, with no reported medical history and no concomitant medication, who took 1 tablet of [redacted] as post coital contraception, 3 days and 2 hours after an unprotected sexual intercourse. Five days after the first [redacted] ntake, the patient took 2 tablets of [redacted] on the same day. The day after, a pregnancy at 2 weeks and 6 days was diagnosed by a home pregnancy test. After unsuccessful follow-up attempts, the case was considered as lost to follow-up and the outcome of the event was considered as unknown. Of note, this pregnancy case was classified with both a potential LOE with insufficient information excluding a pre-existing ongoing pregnancy at the time of [redacted] intake and an inadvertent exposure during pregnancy (due to several intakes).
- A non-serious pregnancy report was received from a consumer and involved a female patient of unspecified age, weight over 76 kg, with no reported medical history or concomitant medication. The patient took 2 tablets of [redacted] as post emergency contraception, as she was "just over 12 stones (76 kg)", as reported (incorrect dosage administered). On unspecified date after [redacted] intake, the patient discovered she was pregnant (method of diagnosis and stage of pregnancy not reported). After unsuccessful follow-up attempts, the case was considered as lost to follow-up and the outcome of the pregnancy was considered as unknown. Of note, this pregnancy case was assessed as unclassifiable (i.e., the information was insufficient to allow any relevant assessment or classification).
- A non-serious spontaneous case report was received from a consumer and involved a female patient of unknown age, with no reported medical history of concomitant medication. On an unknown date, the patient took 2 tablets o [redacted] as emergency contraception, and, after an unspecified time, she experienced a menstruation delay of 18 days. She performed four pregnancy tests which were all negative. After unsuccessful follow-up attempts, the case was considered as lost to follow-up and the outcome of the event was considered as unknown.

In Norway there were 0 cases among 422,711 uses (0%) following reclassification, indicating a low risk of intentional overdose in the pharmacy setting and no increase in risk in the GSL like setting.

The MAH has stated that some clinical studies have involved the intake of [redacted] at single dose up to [redacted] and there have been no AEs reported in these studies.
Since this product has been available since [redacted] 9 cases of "Incorrect dosage/dose administered" (i.e., cases with [redacted] intake of more than 1 tablet at once) and 8 “Intentional product misuses” were reported spontaneously to [redacted]

Based on the misuse surveillance program conducted by the MAH using a multi-faceted approach to try to detect any signal of the misuse of [redacted], drawing data from the USA, where [redacted] is available by prescription, as well as from selected EU countries where [redacted] is available as an OTC product did not provide evidence of any signal suggesting that women are misusing or seeking to misuse [redacted] by using multiple tablets in pregnancy, nor that the product is being systematically misused even as defined by the secondary misuse endpoints.

Expert Opinion:

The likelihood that there would be an increase in intentional overdose if [redacted] were available as a GSL medicine was considered non-existent to low (mean score 0.8), with minimal clinical impact (mean score 0.8). The total risk attribute score was 0.64).

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk related to intentional overdose, the dose (one tablet) has been included clearly on the label. Experts agreed this was adequate and nothing further would be needed.

Assessor's comment: Although the GSL availability of [redacted] would mean that the medicine can be bought without any medical supervision, it is unlikely that women would choose to purchase and take more than one tablet of [redacted] per UPSI. There may be several reasons for this including the cost ([redacted]).

The information on the label which emphasises the dose is considered to be adequate.

5.3.3 Worsened Outcome Due to Self-Management

5.3.3.1 Increased incidence of sexually transmitted diseases (STD), reduced use of condoms

The MAH has stated that there is no evidence to suggest that access to GSL [redacted] would increase the incidence of sexually transmitted infections (STIs) or reduce the use of condoms.

In a 6 month follow up study, advance provision of EHC to adolescents (aged 15-20 years) was not associated with more unprotected intercourse or less condom or hormonal contraception use. Similarly, results from a meta-analysis showed advance provision of emergency contraception did not negatively affect sexual and reproductive health behaviours and outcomes compared with conventional provision. A qualitative study found women who were provided with advance EHC would not take risks with contraception or STIs.

Expert Opinion:

Experts considered it unlikely that GSL access to [redacted] would lead to an increased risk of STIs and a reduced use of condoms (mean score 0.6) and that this would have a low clinical impact (mean score 1.4). The overall risk attribute score was 0.84.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk of an increased incidence of sexually transmitted disease or reduced use of condoms, a warning has been included on the label which states:

- '*As you had unprotected sex, you may have been exposed to sexually transmitted infections.* [redacted] *will not protect you.'*

The experts considered that the mitigation information should be included in the PIL, not the label.

Assessor's Comments:

It is agreed that it is unlikely that the GSL availability of [redacted] would directly increase the risk of STIs and reduce the usage of condoms. However the inclusion of this warning is not considered to be necessary on the label, as this information is not essential for a woman to know before she takes the medicine.

5.3.3.2 No 'preventive' services by seeing HCP
The MAH has stated that there is no evidence to suggest that access to [redacted] as a GSL medicine would directly prevent access to other preventive services (i.e., sexual health services), which women and adolescents may use to access EHC or other sexual health services for free.

The NGOs interviewed for this application recognised that GSL supply would mean there was not an opportunity for a HCP to provide additional information or advice. However, [redacted] stated that they believe "information [about contraceptive options] should be optional and provided at the woman's request, in the same way that's available via healthcare professionals when accessing any form of medical care or medication."

[redacted] expressed a concern that GSL reclassification would mean "an opportunity to discuss ongoing contraception – especially for people accessing EHC multiple times – may be lost." Under current provision routes, this organisation states best practice is to provide EC alongside the offer of quick start contraception (progesterone-only pill) and/or information and advice about other contraceptive methods and screening for STIs. The organisation recommended that to mitigate this risk in the GSL setting, links should be provided to reliable sources of information on contraceptive choices, as well as information about local sexual reproductive health provision and provision of quick start contraception from the pharmacist.

Expert Opinion:

Experts thought that the interaction between pharmacists and women requiring preventive services (including ongoing contraception) may not be optimal (as indicated in the mystery shopper studies) but that there was a moderate to high likelihood of a decrease in use of 'preventive' services (including ongoing contraception options) if [redacted] were available as a GSL medicine (mean score 2.2). However, it was considered that this would have a low/unimportant clinical impact (mean score 1). The total risk attribute score was 2.2.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk of a reduction in 'preventive' services, the warning related to speaking to a healthcare professional about regular contraception and alternative contraceptive methods has been included ('*if you wish to consider alternative contraceptive methods, talk to a healthcare professional to choose one that is suitable for you').*

Assessor's comments: There is a risk that the GSL availability of [redacted] may change the public's attitudes to EHC over time and the use of the medicine may be regarded as less of an 'emergency use'. This is particularly relevant to adolescents or women who have never used EHC or other forms of contraception before.

The presence of a pharmacist reminds women that they should use a regular method of contraception that is suitable for them. They are well placed to signpost to sexual health clinics or services that some women may benefit from. However in the absence of a pharmacist, this important information is unlikely to be conveyed to a woman, which may in time result in the frequent use of EHC, possibly due to less information being provided about other types of contraception.

5.3.3.3 No informed choice of EC options because the customer is not seeing a HCP
The MAH has stated that there is no evidence to suggest that access to [redacted] as a GSL medicine would decrease a consumer's ability to make an informed choice regarding EC.

The MAH has referenced the use of EHC in Germany where since March 2015, 'doctors, particularly gynaecologists, continued to play an important role for users of oral EHC. Women sought HCP advice either for a prescription when OTC status was not known, for prescription reimbursement, to have an unintended pregnancy ruled out, or perhaps most importantly, as the main source of information about EHC (44% of women sought advice via this route).'

[redacted] stated that "placing products on the shelf does not mean people cannot consult with their pharmacist about the most appropriate product for them and how to use it; it simply means that this consultation is not mandatory."

Expert Opinion:

Experts considered that there was a low to moderate likelihood that availability of GSL [redacted] would result in a decrease in a woman's ability to make an informed choice of EC options (mean score 1.4) but that this would have a low/unimportant clinical impact (mean score 0.8). The overall risk attribute score was 1.12.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk related to a reduced ability to make an informed choice of EC options by seeing HCP, a statement around use of the copper IUD is included within the leaflet. Experts agreed this was adequate and nothing else needed be added.

The MAH was also requested to include a reference on the label about the course of action to take if UPSI or contraceptive failure occurred [redacted] It is important that these women are signposted to seek medical advice, which would reflect the advice provided by a pharmacist in a P setting. Therefore the following statement has been included on the label:

'If the unprotected sexual intercourse occurred [redacted] before [redacted] intake, you are advised to seek medical advice'.

Assessor's comment: A current role of the pharmacist in supplying [redacted] as a P medicine is to discuss EHC choices with a woman to determine which would be the best option for her. The current pharmacy training booklet includes information to educate pharmacists about the differences between different EHC methods so they can advise the woman accordingly. However in a GSL setting, women may not need to know the difference between [redacted]

More importantly, the first question asked by a pharmacist when women present for EHC in a pharmacy is how long ago UPSI occurred. If women had UPSI [redacted] pharmacists would signpost them to a doctor or sexual health clinical for an IUD to be fitted. Therefore the proposed statement which signposts women to seek medical advice is considered to be appropriate.

There is however a risk that the GSL availability may result in an assumption that [redacted] is a first line treatment for EC, or even that it is superior to [redacted] or an intra-uterine device. On the contrary, the insertion of an IUD is the most effective form of EC, and pharmacists are well placed to discuss this option with women, particularly if they request EHC on multiple occasions.

5.3.3.4 Consumer does not take appropriate actions after using EHC and unintended pregnancy occurs

The MAH has stated that there are a number of important actions that may need to be taken after using EHC and failure to take these actions can result in unintended pregnancy. These include:

• Another tablet is not taken when vomiting occurs within 3 hours of intake

• Barrier method not used for remainder of menstrual cycle

• A pregnancy test is not performed if period is more than 7 days late

• Doctor is not seen if pregnancy occurs

The MAH considers that there is no evidence to suggest an increased likelihood of women not taking appropriate actions after using [redacted] in a GSL setting and an unintended pregnancy occurring.

Expert Opinion:

The experts agreed that the risk of unintended pregnancy occurring as a result of inappropriate actions after taking [redacted] would not be very different between the P and GSL settings. Overall, the experts agreed that there was a low likelihood that an individual woman would not take appropriate actions after using EHC if [redacted] were reclassified to GSL (mean score 1), and that this would have a low to moderate impact (mean score 1.4). The overall risk attribute score was 1.4.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk of an unintended pregnancy occurring as a result of a failure to take appropriate actions with GSL [redacted] the following has been included on the label:

- If you vomit within 3 hours of taking the tablet, take another tablet as soon as possible
- If you are currently taking hormonal contraception, continue to use it as usual after taking the tablet, but also use condoms every time you have sex until your next period starts
- You should use condoms every time you have sex after taking [redacted] until your next period starts. In case you have unprotected sex again before your next period, you can take another [redacted]
- If your period is more than 7 days late; if it is unusually light or unusually heavy; or if you experience symptoms such as stomach pain, breast tenderness, vomiting or nausea, you may be pregnant. You should do a pregnancy test right away. If you are pregnant, it is important that you see a healthcare professional.

Assessor's comment: The proposed warnings on the label may help to minimise the risk of an unintended pregnancy occurring after taking [redacted] However, there is still a concern that as a GSL medicine, this information may not be read if the tablet is quickly purchased and taken (which is likely to occur as women are aware that the tablet should be taken as quickly as possible). In a P setting, pharmacists and pharmacy staff notify women of all of the above points as part of their standard consultation, so that they are aware of this before

being supplied with [redacted] Therefore whilst this information has been included on the label, it is not convincing that this could replace the role of a pharmacist.

5.3.3.5 Increased unprotected sex due to advanced supply of [redacted]

The GSL availability of [redacted] would allow the product to be purchased in advance. This could be purchased by women of all ages, including adolescents under the age of 16, and also men.

The risk associated with purchasing [redacted] in advance is that it could potentially increase the frequency of unprotected sex. This may change attitudes towards to the pill, i.e. it could be regarded less of an emergency use.

Currently, pharmacists can provide EHC in advance but only for exceptional circumstances once it is deemed to be safe and appropriate. Pharmacists would use their professional discretion to determine whether the advanced supply would be suitable.

However, the MAH considers that there is no evidence that the incidence of unprotected sex would increase i [redacted] were available as a GSL medicine.

The MAH has cited several studies which have shown that providing advance access to EHC does not lead to increased frequency of unprotected intercourse, or less condom or hormonal contraception use, compared with conventional provision, and does not lead to risk taking behaviour regarding the use of contraception or contracting STIs.

Expert Opinion:

Available evidence suggests that GSL access to [redacted] tablets is unlikely to increase the incidence of unprotected sex (mean score 0.8) and experts agreed this would have a moderate clinical impact (mean score 1.8). The total risk attribute score was 1.44.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk related to increased incidence of unprotected sex, the warning has been included on the label which states that [redacted] should not be used as a regular contraceptive and that it is for occasional use only.

Assessor's comment: It is unlikely that the GSL availability of [redacted] would result in increased UPSI. This is mainly due to the cost of the product, which is likely to deter women from using [redacted] as a regular contraception.

5.3.3.6 Lost opportunity for safeguarding (i.e., use in vulnerable/abused women (all ages))

The MAH has cited a recent study which has shown that women who experience domestic violence and abuse (DVA) are twice as likely to seek EHC than their peers, often as the only action a woman can take to prevent pregnancy when experiencing reproductive coercion.

In the current pharmacy supply model for EHC, there is an opportunity for pharmacists to assess whether the woman may be a victim of domestic violence or abuse or to assess other vulnerability and to implement the appropriate safeguarding measures. In a GSL setting, there is no HCP to implement safeguarding.

The MAH considers that the controlling nature of these women's relationships may present a barrier to them having access to other forms of birth control, thus making EHC a more attractive contraceptive option. Attending appointments at sexual health clinics and consultations with pharmacists can involve lengthy waits and can be impossible if the abuser is with/near women. Being able to take EHC off shelf in pharmacy or supermarket may make access possible.

The pharmacy organisations interviewed for this application highlighted the missed opportunity for safeguarding as one of their key concerns/objections to making [redacted] available as a GSL medicine however they also stated that encountering a woman in pharmacy who needed safeguarding was rare. Moreover, availability of [redacted] as a GSL medicine does not mean that vulnerable women have no other recourse to help. The Domestic Abuse Campaign, 'Ask for Ani' (Action Needed Immediately) to enable victims of domestic abuse to access immediate help from the police or other support services from the safety of their local pharmacy was launched in early January 2021 across the 2,300 Boots stores and 255 independent pharmacies. From January to June 2021, the pharmacy organisation supporting the Home Office in this scheme reported 79 instances in which people experiencing domestic abuse had sought help in pharmacy.

The 'Ask for Ani' campaign is independent of any product/type of product so will continue to be accessible to women whether or not they access EHC in pharmacy or in a supermarket.

By contrast, the NGOs interviewed for this application, were strongly of the opinion that the benefits of increased access resulting from GSL status, particularly for vulnerable or abused women, outweighed the potential missed opportunity for safeguarding in pharmacy. *"Well-trained pharmacists who are equipped to safely ask about domestic abuse may be able to identify survivors, respond to disclosure in a supportive way and ensure they are to access the specialist services they need to escape and recover."* However, as "*there is little evidence to suggest that these consultations currently identify a significant number of women experiencing domestic abuse, we therefore do not consider that this risk outweighs the benefits [of GSL reclassification]."*

[redacted] added that "*the worst possible outcome for somebody who is at risk of becoming pregnant as a result of abuse or sexual assault is that they are denied access to emergency contraception because they may be unwilling to discuss the circumstances surrounding their presentation in a pharmacy-based situation*." They highlighted that consideration regarding outcomes must also be considered in relation to what happens if women and girls who have experienced sexual abuse are unable to access EHC as required.

Expert Opinion:

The experts agreed that there was a low likelihood that use of [redacted] by individual vulnerable women whose vulnerability/risk was not identified (safeguarding), would increase if [redacted] were reclassified to GSL status (mean score 1) and that this would have a low to moderate clinical impact (mean score 1.6). Total risk attribute score 1.6.

Proposed mitigation measures:

The MAH has stated that in order to mitigate any potential risk related to use in vulnerable/abused women, information has been included on the label which signposts vulnerable women, including women subject to domestic violence, sexual abuse and adolescents aged less than 18 to helplines for further advice. Additional information has also been included in the leaflet on these issues.

Assessor's comment: As cited by the MAH, a recent study has shown that women who are exposed to domestic violence and abuse (DVA) are twice as likely to seek EHC than unexposed women. A consultation for EHC is an appropriate context for asking about DVA, responding supportively, and offering referral to specialist DVA services. As a GSL medicine, the opportunity for a consultation to occur is lost, thereby increasing the risk of identifying a case of DVA.

The absence of a pharmacist to implement safeguarding is a major risk associated with this reclassification. The MAH has stated that the intervention of a pharmacist to safeguard vulnerable women is likely to be rare. Whilst the likelihood of this risk cannot be established, a medicine is not suitable for GSL classification if there are greater safeguarding concerns than when it was available as a P. Furthermore, there is a risk that over time, the purchasing of EHC from retail outlets such as supermarkets and petrol stations will replace seeking advice from a healthcare professional due to the convenience of the GSL availability of [redacted] This could result in women who are subject to domestic violence or sexual abuse delaying seeking advice or support. [redacted]

Pharmacists are well placed to assess women before supplying EHC. The pharmacy consultation provides an opportunity to assess whether a woman is anxious or is showing any additional signs of abuse. [redacted] Pharmacists can also provide the support by reminding women that their consultation is confidential and that support can be provided if needed.

The MAH considers that the opportunity to buy [redacted] on behalf of someone else would be of benefit to women who are victims of domestic violence and sexual abuse as they may be able to ask a friend or relative to purchase it if they cannot get access to it. However, this could potentially result in women taking a medicine which may not be suitable for them. Purchasing [redacted] on behalf of someone else increases the risk of missing important information on the label and may lead to inappropriate use.

Pharmacists currently assess women on a case-by-case basis to determine whether they would be suitable to take EHC, and also tailor advice to them based on their needs, e.g. recommend starting a regular contraception. The absence of a pharmacist would result in a lost opportunity to provide additional support or advice which could be of use to a woman.

Overall it is considered that the risk of a missed opportunity for safeguarding cannot be replaced with the information on the label or in the leaflet.

5.3.3.7 MAH's conclusion on 'risk of misuse'

The MAH has stated that despite the Royal College of Obstetrics and Gynaecology's unequivocal recommendation as part of the national women's health strategy to ensure that oral EHC is reclassified to GSL (Annex 5), the UK pharmacy organisations interviewed for this application expressed concerns about the risks of supply without the supervision of a healthcare professional and did not support GSL supply. Pharmacy organisations placed high value in the 'wrap-around services' provided by pharmacists during the provision of EHC, including the ability to support informed choice, impart public health advice, signpost to other services and answer questions. In addition, they did not feel that written information could overcome two of their key concerns:

• Safeguarding

• Referral network pathways and safety net

The MAH has stated that for all the identified risks outlined in their application, including the concerns raised by the pharmacy organisations, the clinical experts' opinion was that the incremental risks associated with a GSL setting were minimal and/or unlikely to occur, and that the proposed pack and leaflet would adequately minimise these risks.

The NGOs interviewed for this application expressed a range of opinions. The NGO representing women experiencing domestic violence felt that the benefits of increasing access to EHC for women who are unable to or prefer not to access it using currently available supply options, significantly outweigh the potential risks.

[redacted] could see some advantages but were concerned to ensure that women did not miss opportunities to receive advice and support. [redacted] were strongly in favour of GSL supply: "*There are no known health risks associated with the use of progestogen-based EC. No deaths or serious complications have been causally linked to this product, and the World Health Organisation classifies it as a Level One medication – indicating there should be no restrictions on its use. Emergency contraception meets all the criteria to be classified as a medication that can be sold directly off-the-shelf without a consultation, as it is in other countries."*

5.3.3.8 Assessor's comments on 'risk of misuse'

The most important risk associated with this reclassification is the lost opportunity for safeguarding. The presence of the pharmacist in the current supply of [redacted] is considered to be essential for women who may have been domestically abused, subject to sexual violence, or are vulnerable, [redacted] Whether this intervention is rare or not, pharmacists are well-placed in the community setting to provide advice and support and to refer if appropriate. There is a risk, [redacted] that the required support to safeguard these individuals will be unavailable. This may result in women and young adolescents continuing to purchase EHC from retail outlets when they have been abused, which may delay seeking help from a healthcare professional.

It is unlikely that women will intentionally choose to use [redacted] as a regular method of contraception, mainly due to the cost and the inconvenience of the pack size. Other hormonal contraception is often available without a charge and provide one month's supply of contraception.

The main risk associated with unintentional misuse is the risk of drug interactions occurring. Women often purchase EHC when they are feeling anxious or concerned, and it is likely that they may take the tablet in a timely manner, particularly because many women are aware that EHC should be taken as soon as possible after unprotected sex. This may result in important information such as interacting medicines to be missed. The consequence of this interaction is an unintended pregnancy which is considered to be a significant risk. The presence of a pharmacist in the current supply of [redacted] as a P medicine would ensure that a woman is asked important questions, e.g. any medication that is currently being taken, before [redacted] s considered suitable to take.

The other risks associated with this medicine as a GSL product are related to the worsened outcome due to self-management.

The presence of a pharmacist reminds women that they should use a regular method of contraception that is suitable for them. They are well placed to signpost to sexual health clinics or services that some women may benefit from. However in the absence of a pharmacist, this important information is unlikely to be conveyed to a woman, which may in

time result in the frequent use of EHC, possibly due to less information being provided about other types of contraception.

Some risks such as the risk of an unintended pregnancy occurring due to the failure of taking appropriate actions after UPSI could be prevented if the information on the outer carton is adhered to. However, this risk is still relevant and it is extremely unlikely that the information on the label could replace the role of a pharmacist in conveying this important information.

The 'risk of misuse' aspect of the GSL criterion has not been met.

5.3 Special Precautions in Handling

There are no special precautions required in handling [redacted] therefore this aspect of the GSL criterion has been met.

5.4 Wider sale would be a convenience

The MAH has highlighted the benefits and risks of the GSL availability of [redacted] which are outlined below.

Improved access:

- More widespread availability
- Enabling Emergency Hormonal Contraception (EHC) to be taken sooner after unprotected sexual intercourse (UPSI)
- Increased usage (when required)
- Availability for others to purchase (i.e., partners, friends, parents)
- Removal of pharmacy consultation as barrier to access
- Increased ease of access to supply ahead of use
- Better access to more effective oral EHC
- [redacted]

Improved clinical outcome

- Increased likelihood of preventing unintended pregnancy in individual women
- Increased efficacy due to increased ability to take EHC within 24 hours of UPSI

Improved Public Health

- Potential reduction in the number of unintended pregnancies at public health level
- Potential decreased abortion rate and maternal consequences of abortion
- Additional time for pharmacists to offer other services that improve public health (i.e., smoking cessation)
- Destigmatisation of EHC

Enhanced consumer involvement

- Improved autonomy to make own reproductive health decisions

Economic benefit

- Potential reductions in NHS costs associated with provision of abortion
- Economic outcomes associated with prevention of unintended pregnancy

Benefits:

5.4.1 Improved access

5.4.1.1 More widespread availability
The MAH considers that access to [redacted] as a GSL medicine would allow:

- Availability in a wide range of retail outlets which have increased opening hours. Although some pharmacies have extended opening hours, this is not universal and access to EHC from a pharmacy at the weekend, on bank holidays or late at night may be particularly difficult in smaller towns or rural areas, meaning that some women are unable to access treatment as quickly as they would like (see results from Omnibus survey below).

Omnibus Survey
The MAH has summarised the results of a recent survey of (760) women aged 16-54 in England, Scotland and Wales below.

In this research, 60% of women who had experienced unprotected sexual intercourse and wanted to use EHC, had not accessed it from a pharmacy. 45% of these women had not been to a pharmacy for EHC because they felt embarrassed, were concerned about privacy, were afraid they would feel judged, or because a previous experience in pharmacy had been negative. Whether or not they have previously used EHC, the survey concluded that women were reluctant to access EHC in pharmacy because: they are concerned about privacy (46%, n=223); they would have to answer intimate questions (48%, n=233); or they would feel judged (44%, n=217). Most women (77%, n=369) would feel more comfortable accessing EC from a supermarket where there is no requirement for a consultation.

The MAH has stated that women want to be able access to EHC from shops like supermarkets as well as from their GP, sexual health clinic or pharmacy and for some women, access via a supermarket would be their preferred option.

In the most recent study conducted amongst sexually active women aged 16 to 54 years, if it were available: 47% would obtain EHC free from their GP; 53% would go to the pharmacy if EHC could be obtained free with a pharmacy consultation; 41% would pay for EHC in pharmacy with a consultation; and 42% would buy EHC from a supermarket with no requirement for a consultation. The preferred route of access for EHC would be: from their GP for 11% of women; free in pharmacy for 20% of women; purchased in pharmacy for 12% of women; and purchased in a supermarket for 16% of women. Furthermore, one quarter said that they would not find it easy to get to a pharmacy for EHC at whatever day or time of day they needed it.

The MAH has further stated that barriers to gaining timely access to EHC is stressful for women, many of whom understand that they need to take EHC as soon as possible following UPSI. Most women said that GSL supply would make it significantly easier for them to access EHC when they needed it (79%, n=381), and that they would be able to access EHC sooner than via the other supply routes (84%, n=400).

The study also indicated that around one third said that they would be more likely to purchase in advance to ensure that they could use EHC as quickly as possible after UPSI. Their reasons for advance purchase were to: enable them to use EHC as quickly as possible if it was needed (54%, n=152); be prepared just in case of UPSI (45%, n=125); to take on holiday in case of UPSI (26%, n=73); and to have available in case a friend or family member needed to use it (41%, n=113).

Furthermore, 59% (n=284) said that if EHC were available as a GSL medicine, they would ask someone to purchase EHC on their behalf and 82% (n=398) would purchase for someone else.

78% (n=376) said that GSL availability would make them feel more in control of their reproductive health.

Overall, the MAH has stated that :

- Access to pharmacies has recently been limited due to the COVID-19 pandemic
- Consultation experience is not always a positive one
- Privacy of consultation rooms is not always guaranteed
- Women can feel embarrassed in pharmacies
- Interaction with a pharmacist is not preferred as women may feel judged (Most women feel more comfortable accessing EC from a supermarket where there is no requirement to engage with an HCP)

Expert opinion

The expert panel unanimously agreed there would be a high likelihood of [redacted] being more widely available for an individual woman (especially those who are reluctant to use current supply options, or who have difficulty accessing current supply options) if available as a GSL medicine (mean score 3 = high likelihood), and this would have a moderate to high (mean score 2.6) clinical impact in decreasing the risk of unintended pregnancies at an individual level. These scores lead to a final attribute score of 7.8.

Assessor's Comments: A P-GSL reclassification would inevitably result in an increased access to the medicine. However the risks associated with increased access, such as an absence of safeguarding vulnerable individuals and referring to appropriate pathways outweigh the benefits outlined by the MAH above. It is concerning that from the surveys cited by the MAH, 113 women stated that they would buy [redacted] to have available in case a friend or family needed it, and that 393 women would purchase [redacted] on behalf of someone else. This demonstrates that the GSL availability could undermine the importance of the medicine, and the specific advice associated with it.

5.4.1.2 Enabling Emergency Hormonal Contraception to be taken sooner after unprotected sexual intercourse (UPSI)

The MAH considers that:

- Availability from other retail outlets which have increased opening hours may mean that women can access EHC sooner
- A recent mystery shopper survey indicated that around 1 in 5 mystery shoppers left without obtaining EHC at all (e.g., being told that EHC was not in stock; that they needed to come back later; that no trained pharmacist was available to provide EHC, or that a copper intrauterine device would be more effective). The authors of this study concluded that pharmacies were unable to "maximise timely access" for EC
- Women may be able to purchase EHC in advance to ensure they can use it as soon as possible after UPSI
- For women experiencing domestic abuse who may be prevented from travelling, accessing public services or leaving the house alone and therefore unable to access EHC themselves, GSL supply would facilitate timely access to EHC, enabling friends and family to purchase EHC as soon as possible after UPSI

Expert opinion
The experts agreed there was a moderate to high likelihood of an individual woman taking [redacted] sooner after UPSI if available as a GSL medicine (mean benefit score 2.8/3) and that the clinical impact for [redacted] being taken sooner after UPSI would be a potential decrease in the number of unintended pregnancies and abortions (mean score 2.6/3). These scores lead to a final attribute score of 7.28. Experts suggested that both the likelihood of occurrence and subsequent clinical impact would be dependent on the woman's knowledge that [redacted] is available GSL and the cost of the product.

Assessor's Comments: It is agreed that the increased access to [redacted] as a GSL medicine may increase the likelihood of taking the tablet sooner, which could in turn reduce the likelihood of pregnancy. However this is also based on a person understanding the information, such as when [redacted] is effective, and taking the medicine appropriately in order for it to work effectively. The presence of a healthcare professional, i.e. a pharmacist, is considered to be of utmost importance, particularly for vulnerable individuals or first-time users of EHC.

5.4.1.3 Increased usage (when required)
The MAH considers that:

- The current uptake of EC is low in the UK; nearly three-quarters (73%) of women aged 18-35 who had unprotected sex in the last year did not seek EHC, despite not wanting a pregnancy (from a sample of 1036 women)

- Transgender individuals presenting as a male may not be able to discuss contraceptive needs in a safe environment, and may be refused EHC on grounds of their appearance, although they may have intact pelvic organs with a potential for pregnancy.

- Women in the UK who are experiencing domestic violence and abuse may have an increased need for EHC. A systematic review found that intimate partner violence and reproductive coercion increased the odds of using EHC

Expert opinion
The experts agreed a moderate to high (mean score 2.6) likelihood of an increased usage of [redacted] for an individual woman who needed EHC if available as a GSL medicine and that this would have a moderate to significant clinical impact (mean score 2.6). These scores lead to a final attribute score of 6.76.

Assessor's Comments: There may be a number of reasons why women may not be taking EHC, e.g. cost, personal views on contraception etc. Therefore the potential increase in usage is not considered to be a benefit of this reclassification, as the current usage levels are not directly related to the access of the medicine. [redacted] is classified as a pharmacy medicine, so there is already considerable access to it, and there is an opportunity for transgender individuals to seek EHC from numerous sexual health clinics if required.

5.4.1.4 Availability for others to purchase (i.e., partners, friends, parents)

The MAH considers that:

- As there are currently barriers to access for EHC, e.g. concerns about privacy, stigmatisation and embarrassment, a woman requesting a partner, friend or parent to purchase EHC for them, without the need for a pharmacist consultation could remove that barrier and increase uptake of EHC.

- This could be particularly valuable for women experiencing domestic abuse who may be prevented from travelling, accessing public services or leaving the house alone and therefore unable to access EHC themselves.
- Men may be able to purchase EHC.

Expert opinion

The experts noted that if [redacted] were available as a GSL medicine, there would be no need for the pharmacy consultation, which could mean some women would be more comfortable buying it themselves. However, experts did think that in the UK, partners, parents or friends would also purchase EHC. Experts agreed a moderate to high likelihood of an increased opportunity for others to purchase [redacted] if available as a GSL medicine (mean score 2.4), and this would have a moderate to significant clinical impact (mean score 2.4). The final benefit attribute score was 5.76.

Assessor's Comments: The availability for others to purchase presents a significant risk and is not considered to be a benefit of this reclassification. There is a risk that adolescents less than 16 who may have been sexually abused and may require support/safeguarding could ask a friend or relative to purchase [redacted] on their behalf. This removes the opportunity for any safeguarding or referral pathways which may have been useful for a vulnerable individual.

Also, the current supply of [redacted] is based on a number of questions which a pharmacist asks, such as whether the woman is taking other medication, whether they could already be pregnant etc. There is a risk that the purchase of [redacted] by a family member or friend may result in key advice and information being missed. This further reinforces the importance of including all essential information on the label.

5.4.1.5 Removal of pharmacy consultation as barrier to access

The MAH considers that:

- Women feel embarrassed, want to remain anonymous and have concerns over privacy
- The proposed labelling could adequately minimise any risk in the absence of the pharmacist. Only a small proportion of more complicated cases would require the intervention of a pharmacist or other HCP, but these women would most likely already be under medical supervision.
- Women who are at risk of becoming pregnant following sexual assault or domestic violence would benefit from easier access to EHC as they may be unwilling to discuss circumstances around their presentation in a pharmacy environment
- Trained pharmacists may not always be available

Expert Opinion

The experts unanimously agreed that there was a high likelihood that removing the requirement for a pharmacy consultation through GSL availability of [redacted] would improve access to [redacted] for an individual woman (mean score 3), and this would have a moderate to high clinical impact in reducing unintended pregnancy (mean score 2.6). These scores lead to a final benefit attribute score of 7.8.

Assessor's Comments: The benefit of the presence of a pharmacist, particularly the advice and support for safeguarding vulnerable individuals, outweighs the 'barrier' of a pharmacy consultation. The GSL availability of [redacted] will be dependent on whether the GSL criterion is met, in particular, whether there is a minimal hazard to health and risk of misuse. The concerns raised over privacy and feeling embarrassed are of little relevance in determining whether this product would be suitable as a GSL medicine.

5.4.1.6 Increased ease of access to supply ahead of use

Currently only a small proportion of women purchase an advanced supply of EHC, which is based on a pharmacist using their professional judgement to decide whether the benefit of advanced supply would outweigh any risks. The MAH considers that advance supply:

- does not encourage risky sexual behaviour among young people and is therefore recommended
- could shorten the time between UPSI and EHC use
- does not lead to increased frequency of unprotected intercourse
- does not lead to increased rates of STIs

GPs and clinics are allowed to prescribe EHC in advance only for specific reasons (e.g., travelling abroad and relying on condoms). Pharmacy schemes which offer free EHC may not supply it for advance use due to limited funding. Pharmacy retail purchase of EHC does allow for advance purchase at the pharmacist's discretion, but pharmacists may not feel comfortable with this.

UK Pharmacy Organisations reported that advanced supply of EHC from pharmacies is uncommon because:

- In many areas supervised consumption is part of the service specification (i.e., local patient group directions (PGD)), to ensure that the person obtaining the EHC is the end user
- Pharmacists may be uncertain about the product licence for advance supply
- Advance supply may raise safeguarding concerns (despite the evidence showing it does not lead to an increase in risk taking behaviour as mentioned earlier)

Expert Opinion

Although supply ahead of use requires people to know about GSL EHC and to be somewhat organised, the experts agreed a moderate to high (mean score 2.6) likelihood of an increased ease of access to supply in advance of need of [redacted] for an individual woman if available as a GSL medicine, and that this would have a moderate (mean score 2.2) clinical impact. These scores lead to a final attribute score of 5.72.

Assessor's Comments: There are a number of risks associated with the advanced supply of [redacted] and therefore this is not considered to be a benefit of this reclassification. There is a risk that [redacted] may be bought in advance for someone where use of the medicine would be unsuitable, and could impact the efficacy of the medicine (possibly resulting in an unintended pregnancy). There is also a risk that the medicine could be bought by an abuser or perpetrator, where there would be no opportunity to safeguard a vulnerable person.

6.4.1.7 Better access to more effective oral EHC

The MAH considers that:

- There is evidence that demonstrates that [redacted] is a more effective method of EHC [redacted] especially when taken close to ovulation and within the first 24 hours after intercourse

Expert Opinion

The experts did not reach a consensus for the likelihood (1 vote for score of 1; 2 votes for score of 2; 2 votes for score of 3) or clinical impact (1 vote for score of 1; 3 votes for score of 2; 1 vote for score of 3) of better access to more effective oral EHC for an individual woman if [redacted] was available as a GSL medicine, as they believed it could depend on issues such

as the relative price of [redacted] These scores lead to a final benefit attribute score of 4.4.

Assessor's Comments: The effectiveness of [redacted] is not considered as part of this reclassification.

[redacted]

5.4.2 Improved clinical outcome

5.4.2.1 Increased likelihood of preventing unintended pregnancy in individual women

The MAH considers that:

- A prevention of a pregnancy would result in both psychological and physical benefits for women
- Abortions can be an unpleasant and a stressful experience for women
- Unintended pregnancies can lead to a number of complications

Expert Opinion

The experts agreed a moderate to high (mean score 2.6) likelihood of an increased usage of [redacted] therefore preventing unintended pregnancy for an individual woman if available as a GSL medicine. This was rated as having a significant clinical impact (mean score 2.8). These scores lead to a final benefit attribute score of 7.28.

Assessor's Comments: The availability of [redacted] as a GSL medicine would result in an increased access to the product and a possible reduction in unintended pregnancies. The current role of the pharmacist in the supply of EHC involves checking whether the medicine is suitable and ensuring that the person understands the advice. However in a GSL setting where there is no pharmacist or healthcare professional, there is a risk that the medicine may be taken when not suitable, or a person may not understand the advice on the label, e.g. when the medicine is effective to take. Both of these issues could result in an unintended pregnancy.

5.4.2.2 Increased efficacy due to increased ability to take EHC within 24 hours of UPSI

The MAH considers that:

- The time elapsed since intercourse (coitus treatment interval) is critical since the efficacy of both oral EHC products available in the UK declines with time following UPSI
- Most women, perceiving the high risk of pregnancy, seek EC 24 hours after unprotected intercourse when the efficacy of EC is the highest. However, from the results of the Omnibus survey (760 women) in England, Scotland and Wales, only 25% (n=123) of sexually active women said that they would find it easy to get to a pharmacy for EHC at whatever day or time they needed it
- Increased access resulting from availability of [redacted] as a GSL medicine provides a greater opportunity for women to take the most effective EHC as soon as possible following UPSI

Expert Opinion

The experts agreed a moderate to high likelihood (mean score 2.6) of increased efficacy of [redacted] for an individual woman if it were available as a GSL medicine due to increased ability to take EHC within 24 hours of UPSI. This was considered to have a moderate to significant clinical impact (mean score 2.4). These scores lead to a final benefit attribute score of 6.24.

Assessor's Comments: Most women are already seeking EHC within 24 hours of UPSI which demonstrates that access to the product is sufficient.

5.4.3 Improved Public Health

The MAH has stated that unintended pregnancies and childbirths can be distressing, are overrepresented in young women from deprived backgrounds, and can have mental health consequences for women and socioeconomic consequences for women and their families. In 2020, almost 210,000 pregnancies ended in induced abortion in the UK.

5.4.3.1 Potential reduction in the number of unintended pregnancies at public health level

The MAH considers that:

- Wider access may result in a greater benefit as it would be purchasable from a wider range of outlets.

Expert Opinion

The experts agreed a moderate to high (mean score 2.6) likelihood of a potential reduction in the number of unintended pregnancies at public health level if [redacted] was available as a GSL medicine and that this would have a moderate (mean score 1.8) clinical impact. These scores lead to a final benefit attribute score of 4.68.

Assessor's Comments: As outlined in previous sections, it cannot be concluded that the GSL availability of [redacted] would directly reduce the number of unintended pregnancies. This is because the effectiveness of [redacted] is dependent on the understanding of the information on the medicine box.

5.4.3.2 Potential decreased abortion rate and maternal consequences of abortion

The MAH has stated:

- One in five pregnancies in the UK are reported to end in abortion, the great majority of which are unintended resulting from incorrect, inconsistent or non-use of contraception
- Abortion rates are increasing - the largest increases in abortion rates by age are amongst women aged 30 to 34 which have increased from 16.5 per 1,000 in 2010 to 21.9 per 1,000 in 2020
- By contrast, abortion rates for those aged under 18 have declined over the last ten years (from 16.5 to 6.9 per 1,000 between 2010 and 2020). The decline since 2010 is particularly marked in the under 16 age group, where the rates have decreased from 3.9 per 1,000 women in 2010 to 1.2 per 1,000 women in 2020
- Lack of access to EC may subject women to unsafe abortions which contribute significantly to maternal mortality and morbidity

Expert Opinion

The experts highlighted that anything that has an effect to reduce abortion has to be positive, but it would be difficult to quantify the clinical impact. The experts agreed a low to moderate (mean score 1.4) likelihood of a potential decrease in abortion rate and consequences of abortion complications if [redacted] was available as a GSL medicine, and that this would have a moderate to high impact (mean score 2.2). These scores lead to a final benefit attribute score of 3.08.

Assessor's Comments: It cannot be concluded that the GSL availability of [redacted] would directly reduce the number of abortions.

5.4.3.3 Additional time for pharmacists to offer other services that improve public health (i.e., smoking cessation)

The MAH considers that:

- More time could be spent by pharmacists on other health conditions that require more discussion and improving public health such as ongoing contraception, cervical and STI screening, smoking cessation and diabetes awareness.
- One study showed that some pharmacists report that consultations for sexual health issues are time-consuming, stressful and create a time pressure; some pharmacists found it difficult to embed the delivery of sexual health services within the rest of their duties, especially because they could not plan ahead when women would present in pharmacy seeking sexual health services like EHC. In addition, pharmacists found it difficult to deliver sexual health services when staff levels were low or when they were alone in the pharmacy

Expert Opinion

One expert noted (and others agreed) that it was likely that some time would be freed, but there is no guarantee that any 'freed' time would go into public health benefits. The experts were variable in their rating of the likelihood of additional time for pharmacists to offer other services that improve public health (i.e., smoking cessation) if [redacted] was available as a GSL medicine (mean score 2) and this was considered to have a low clinical impact (mean score 1.2). These scores lead to a final benefit attribute score of 2.4.

Assessor's Comments: It cannot be concluded that the GSL availability of [redacted] will directly result in additional time being spent on other public health services. EHC has been available as a P medicine for over 20 years, therefore pharmacists are accustomed to incorporating the provision of EHC into their daily work. The benefit of 'freeing up time' for pharmacists to carry out other services is not relevant and does not outweigh the risks associated with this reclassification.

5.4.3.4 Destigmatisation of EHC
The MAH has stated:

- In a UK survey, several pharmacy users expressed that they felt embarrassed attending for a sexual health issue and were concerned about being judged by other pharmacy clients or pharmacy staff
- Two NGOs interviewed as part of this application ([redacted]) felt there may be a public health benefit regarding destigmatisation of unintended pregnancy and EHC. [redacted] felt that GSL availability would decrease the general public's perceived stigma associated with 'failing' to use contraception and help to normalise self-care in relation to contraception.
- [redacted] stated that reclassification could change attitudes towards EHC generally and with pharmacy staff: "Other medications with a 'P' classification are provided without compulsory and invasive questions - a fact which only serves to strengthen the stigma surrounding EHC and encourages pharmacy workers to consider emergency contraception as a medication and patient population in need of formal oversight."

Expert Opinion
The experts agreed that any stigmatisation would be reduced if [redacted] were available as a GSL medicine but possibly not by a great deal as there were too many factors involved. The experts could not agree on the likelihood of a reduction in stigmatisation of EHC if [redacted] was available as a GSL medicine (1 vote for low likelihood, 3 votes for moderate likelihood and 1 vote for high likelihood, mean score 2). However, they were agreed in this having a low to moderate clinical impact (mean score 1.8) These scores lead to a final benefit attribute score of 3.6.

Assessor's Comments: The presence of a pharmacist and the questions asked during the consultation for the P supply of [redacted] are not considered to contribute to the 'stigma' associated with the medicine. The questions are important to ascertain whether the medicine would be suitable for an individual, to provide important advice which could affect the effectiveness of the medicine, and signpost when appropriate. There are a number of P medicines which involve a consultation with a pharmacist before use, e.g. the supply of sildenafil, desogestrel and estradiol.

5.4.4 Enhanced consumer involvement

5.4.4.1 Improved autonomy to make own reproductive health decisions
The MAH considers that:

- Reclassifying [redacted] to a GSL medicine would give women more control over their reproductive health decisions following UPSI, removing the external influence and time pressures associated with the involvement of pharmacists and sexual health advisors.
- Increased autonomy due to GSL availability may be particularly beneficial for women experiencing reproductive coercion who may be preventing the woman from using a method of contraception.
- Studies investigating advance provision of EHC demonstrate that women are perfectly able to make appropriate decisions about use and to behave responsibly in relation to their sexual and reproductive health when given greater autonomy over their use of EHC
- Other studies have confirmed that women who choose to have advance supply of EHC do not take risks with contraception or sexually transmitted infections (STI)

Expert Opinion
The experts agreed a moderate to high (mean score 2.8) likelihood of an individual woman perceiving increased autonomy to make her own reproductive health decisions if [redacted] were available as a GSL medicine, and that this would have a moderate to significant (mean score 2.4) clinical impact. These scores lead to a final attribute score of 6.72.

Assessor's Comments: This benefit is not specific to this product and is applicable for other P-GSL reclassification applications.

5.4.5 Economic Benefit

5.4.5.1 Potential reductions in NHS costs associated with provision of abortion
The MAH has stated that:

- Abortion due to unintended pregnancy poses a significant financial burden on the NHS.
- Between 2013 and 2020, the additional cost incurred to the NHS from unintended pregnancies amounted to £298.6 million, which includes the 22,036 more NHS abortions a year in 2020
- A reduction in unintended pregnancy with increased availability and use of EHC would not only reduce the clinical burden of abortions on the NHS and on women, but also fits with the government's Public Health Outcomes framework of reducing teenage pregnancies

Expert Opinion
The experts agreed a low likelihood of potential reductions in NHS costs associated with provision of abortion if [redacted] was available as a GSL medicine (mean score 1.4) and that this would have a small clinical impact (mean score 1.6). These scores lead to a final attribute score of 2.24.

Assessor's Comments: It cannot be concluded that the GSL availability of [redacted] would directly result in a reduction in NHS costs. The potential reductions in NHS costs is not within the remit of this reclassification.

5.4.5.2 Economic outcomes associated with prevention of unintended pregnancy
The MAH considers that:

- There is a significant socioeconomic cost associated with unintended pregnancies. More readily available access to preventative measures such as EHC will help mitigate this.
- The use of EHC is in line with governmental family planning guidance

Expert Opinion
The experts agreed a moderate to high (mean score 2.4) likelihood that the economic cost of unintended pregnancies on an individual woman would be reduced, if [redacted] were available GSL, and that this would have a moderate to significant impact (mean score 2.4). These scores lead to a final benefit attribute score of 5.76.

Assessor's Comments: It cannot be concluded that the GSL availability of [redacted] would directly affect economic outcomes associated with prevention of unintended pregnancy. The 'economic benefits' are not within the remit of this reclassification.

5.4.5.3 MAH's conclusion on benefits of reclassification:

The MAH considers that a significant body of evidence suggests that, despite the improved access to EHC afforded by pharmacy supply, many women still face barriers to accessing timely EHC largely due to:

- restricted pharmacy opening hours;
- lack of availability of trained pharmacists at the time they seek help;
- feelings of stigma or embarrassment;
- concerns about privacy.

They consider that the importance of accessing EHC as soon as possible following UPSI to maximise effectiveness is well established and making [redacted] available as a GSL medicine would facilitate this, addressing and overcoming the barriers to access and use. The MAH has stated that GSL provision of EHC has been endorsed by national bodies such as NICE and the RCOG.

According to clinical expert feedback based on the available evidence, availability of [redacted] as a GSL medicine would have a number of important incremental benefits compared with pharmacy supply that would ultimately reduce the risk of unintended pregnancy for women. These benefits are essentially related to overcoming barriers to access to the most effective EHC and enabling it to be taken at the most effective time as soon as possible following UPSI or within 24 hours. They include: more widespread availability (in location and time) and removing the physical and emotional barrier of the pharmacy consultation.

The NGOs [redacted] and an organisation representing victims of domestic violence, considered that making [redacted] available as a GSL medicine would increase access for women who are unable or prefer not to access EHC via existing routes.

6 ROLE OF THE PHARMACIST

The current EU RMP for [redacted] does not include a specific requirement for additional risk minimisation measures (aRMMs), although a pharmacy training material is currently required in the UK for the pharmacy product.

The MAH has stated that the supply of [redacted] in pharmacy usually involves a consultation with a pharmacist who checks suitability of the woman for [redacted] and provides advice about how to take it and what side effects to look out for.

They have further stated that a systematic approach was taken to assess every point of interaction that currently occurs between the pharmacist and customer; to identify every question that is asked and every piece of advice that is given. The objective was to establish what messages would need to be included on the pack or in the leaflet in order to safely replace the pharmacist in a GSL setting. The 'gold standard' of the [redacted] pharmacy training materials (pharmacy guide and checklist) were used as the example of the ideal role the pharmacist should play in the pharmacy supply of [redacted]. The MAH concluded that with the exception of the opportunity of safeguarding which pharmacists report as being rare within a pharmacy, there are no assessments the pharmacist makes and no messages/information he/she provides to customers that cannot be communicated on the carton or in the leaflet.

[redacted] The 'when to refer' section of this guide is a helpful summary of the current role of the pharmacist in the supply of [redacted] as a P medicine.

The role of the pharmacist in the supply of [redacted] is extensive. The MAH was requested to justify how the information on the medicine box could replace the information and advice provided by a pharmacist. The following are considered to be the most important responsibilities which could not be replaced by the information on the medicine box:

- **Safeguarding vulnerable women**

The MAH has confirmed that safeguarding is an issue which cannot be communicated on the medicine box. However this is considered to be the most important issue for a P-GSL reclassification – see section 5.3.3.6. The presence of a pharmacist in the supply of [redacted] would ensure that women who have been a victim of domestic abuse or sexual violence, including young adolescents, are supported and signposted if appropriate.

The presence of a pharmacist is also important for adolescents under the age of 16. Pharmacists must be reassured that this age group are Gillick competent before supplying [redacted]

The MAH considers that in line with the indication, the main focus of safeguarding vulnerable women is the provision of EHC. They have stated that pregnancy is a known risk factor for domestic abuse, and an unplanned pregnancy would likely exacerbate any pre-existing abusive or strained relationship, with both situations putting the unborn child at potential risk. Therefore, the MAH believes that the rapid access to EHC is imperative to the safety and well-being of vulnerable women.

The MAH has stated that they acknowledge the concern about not having a pharmacist interaction, but consider that GSL status would allow the vulnerable women a greater ownership and control of their health, as well as having the opportunity of going to an easily reachable, and familiar 'safe space' of her choosing, e.g. a supermarket.

The MAH has stated that they are very conscious to signpost vulnerable women to appropriate support provides, and have suggested updating the label and leaflet with such wording. They consider that the advantage of including the information on the label as a GSL medicine is that it will be provided universally to all women, which is important as some women may feel uncomfortable having such conversations with pharmacists.

Assessor's comments: It is not agreed that the GSL availability of EHC would manage the safeguarding of vulnerable women. Pharmacists and other healthcare professionals play a crucial role in ensuring the public are safeguarded and referred appropriately. The P-GSL reclassification of [redacted] could [redacted] to purchase the medicine without any medical supervision. This reduced control over the supply of [redacted] is likely to result in greater risks of missing a safeguarding opportunity, [redacted]

- **Advise on the effectiveness of [redacted]**

[redacted] should be used within [redacted] of UPSI or contraceptive failure, and the MAH have outlined this on the medicine box. However, the presence of a pharmacist is important to emphasise the timely manner in which [redacted] should be taken, and to inform women, particularly first time users, that the medicine is more effective the earlier it is taken.

Assessor's comment: Unlike other GSL medicines, [redacted] would need to be taken within a certain time period for it to be effective. The consequence of not taking [redacted] within this timeframe could be an unintended pregnancy. This type of advice is considered essential to highlight to a woman wishing to take EHC.

- **Ascertain whether any interacting medicines (e.g. CYP3A4 inducers) are being taken**

There are a number of medicines which should not be taken together with [redacted]. Whilst other medicines available as GSL include a list of interacting medicines on the label, the consequence of taking an interacting medicine with [redacted] could result in the reduced efficacy of the pill and even an unintended pregnancy. Due to the timeframe within which [redacted] should be taken, there is a risk that some women may miss the information on the medicine box. Therefore the role of the pharmacist in this aspect is considered essential.

Assessor's comment: In a P setting, pharmacists consult with a woman **before** supplying EHC. This ensures that [redacted] is only provided when suitable which reduces the likelihood of the medicine being ineffective, and thereby increases the chances of preventing a pregnancy. The absence of a pharmacist to check for any interacting medicines before a woman takes [redacted] is considered to be a risk, particularly as this list is quite extensive.

- **Confirm whether the woman is already pregnant**

Whilst most women may be aware if they are already pregnant, some women, particularly adolescents, may not be familiar with the signs of pregnancy, e.g. a late period. The consultation with a pharmacist is important so that supply is only made once a pharmacist is reassured that a woman is not pregnant. However, the absence of this consultation may result in women who are already pregnant (but not aware of it) taking [redacted] which will not be effective resulting in an unintended pregnancy.

The MAH is proposing to include 'use in pregnancy or a suspected pregnancy' as a contraindication, however this is not considered sufficient to manage the risk. The MAH have also included [redacted] does not terminate or interrupt an existing pregnancy'.

Assessor's comment: Unlike other GSL medicines, an emergency hormonal contraceptive is likely to be taken quickly. It is therefore likely that women would want to take [redacted] even if they think they are pregnant as they think it may still work.

The inclusion of [redacted] does not terminate or interrupt an existing pregnancy' could result in women taking [redacted] if they have a known pregnancy, as they think it will not have any effect on the pregnancy. This type of advice is not suitable to include on the label as it could undermine the warning to not use if a woman is pregnant.

- **Advise on regular contraception methods**

There is a risk that women, in particular those using EHC for the first time e.g. young adolescents, may not be aware of when to resume regular contraception. Currently, pharmacists advise women that EHC does not contraindicate the continued use of regular hormonal contraception but a barrier method should be used until the next period.

Pharmacists also advise that regular contraception should be continued or started as soon as possible. Therefore there is a risk that in the absence of this information, some women may assume that EHC may work for more than one instance of UPSI in a menstrual cycle, and that no further form of contraception is required. This in turn could lead to an unintended pregnancy.

The MAH have proposed to include advice on the label about using a barrier method until the next period, however this is not considered to be sufficient.

Assessor's comment: In a P setting, pharmacists can advise women, especially women who are not currently using a regular method of contraception, about difference options available to them. This is relevant to women who visit pharmacies frequently to request a supply of EHC, and a P setting is an opportunity for pharmacists to discuss various options with women. Pharmacists can also refer or signpost appropriately if needed.

Although the MAH has proposed including a warning on the label about using a barrier method until the next cycle, this may not be adequate to remind women that [redacted] only protects against one incident of UPSI.

- **Counsel on sexual health**

Pharmacists are well placed to advise women that EHC does not protect against STIs. Some women, especially adolescents, may not be aware of this, and may choose to purchase [redacted] to use instead of a barrier method. Pharmacists can currently speak to women who may be concerned about STIs and refer them appropriately, however in the absence of a pharmacist, women may not know where or how to be referred for support. Therefore there is a risk that women who are concerned that they may have an STI cannot receive the guidance from a pharmacist resulting in a delay in treatment/support.

The MAH has stated that there is no evidence to suggest that GSL access to [redacted] would result in an increased incidence of STIs and a reduced use of condoms. However to manage this risk, a warning has been included on the medicine box about STIs.

Assessor's comment: There is considered to be a risk of women, particularly first time users or young adolescents, taking [redacted] and considering it to be effective against STIs. In a P setting, pharmacists would be available to explain this before supplying [redacted] so that any concerns can be discussed at the time, and appropriate advice and referrals can be made. This also educates women for future instances of sexual intercourse, so that they are aware that only a barrier method would be effective against an STI.

- **Advise on next period**

Pharmacists can currently advise that after taking an emergency contraceptive pill, menstrual periods can sometimes occur a few days earlier or later than expected. If a woman's period is more than seven days late after taking [redacted] or pregnancy is suspected for any other reason, or in the case of doubt, pharmacists would advise the woman to carry out a pregnancy test or visit the GP. The absence of this information before taking [redacted] may have a number of consequences, e.g. women may not inform their GP that they may be pregnant, women may feel concerned about why their period is earlier or later than expected etc. It is important that women are made aware of what to expect with their next period before taking [redacted]

Assessor's comment: The MAH has suggested wording to include on the medicine box to advise women about their next period, however there is a risk that some of this information may be missed. This is because advice concerning actions to be taken **after** intake of the pill are less likely to be remembered if read on a box compared to if a healthcare professional has spoken about this. [redacted] stated that it is likely that the medicine box could be discarded after the medicine is taken. This could result in important actions, such as taking a pregnancy test, being missed.

- **Advise on course of action if vomiting occurs**

If vomiting occurs within three hours of emergency contraception intake it may result in loss of efficacy. Currently, pharmacists advise women that if vomiting occurs within three hours of EHC intake, they should take another EHC tablet as soon as possible.

There is a risk that some women, particularly first time users of [redacted] may consider vomiting to be a side effect of the medicine, which is common with other GSL medicines. This symptom may be ignored resulting in an additional tablet not being taken, which could result in an unintended pregnancy if the first tablet was ineffective.

Assessor's comments: There is a risk that in the absence of a pharmacist, the medicine could be taken without reading the important advice on the box, especially in relation to actions that must be followed after the tablet has been taken. Unlike other GSL medicines, this advice is very important and could affect the effectiveness of the medicine. The advice to take another tablet if vomiting occurs is an example of this. Due to the time sensitive nature of [redacted] it is likely that the medicine could be taken promptly without properly reading the box, or there is a risk that the box could be discarded once the pill has been taken. Therefore, whilst the MAH have included an instruction about taking another tablet if vomiting occurs, this is not considered sufficient to replace the role of a pharmacist.

- [redacted]

The current pharmacy training materials advise pharmacists to 'consider ectopic pregnancy'. In a P setting, the presence of a pharmacist is likely to be useful in communicating signs and symptoms which would require referral to a doctor, e.g. abdominal pain. In the absence of a pharmacist, there is a risk that such symptoms may not be reported to a doctor resulting in delayed treatment. The current [redacted] website states 'Contact your doctor as soon as possible if you think you could have an ectopic pregnancy as it requires medical attention'. The current leaflet states '*As for any pregnancy, your doctor may want to check that the pregnancy is not outside the womb. This is especially important if you have severe abdominal (stomach) pain or bleeding or if you have previously had a pregnancy outside the womb, tubal surgery or long term (chronic) genital infection*.'

Therefore, if women are purchasing [redacted] without any input from a HCP, they would need to be aware of the signs of an ectopic pregnancy. The MAH has proposed wording to be included on the medicine box to manage this risk.

Assessor's comment: Many women may not know the symptoms of an ectopic pregnancy, and there is a risk that this could be missed and not reported in a timely manner. Symptoms such as abdominal pain may be ignored, particularly if a woman or young adolescent is embarrassed to discuss this following UPSI.

- **Advise on general concerns that women may have about EHC**

The current pharmacy training booklet states that use of emergency contraception has no effect on future fertility. This may be a common concern amongst women, and if a pharmacist was present, it would be useful for reassurance to be provided about this concern. The presence of a pharmacist would allow any questions or concerns to be answered allowing a woman to be fully informed before taking [redacted]

Assessor's comment: [redacted] stated that in most consultations for EHC, women have a number of questions to ask. Therefore there is a risk that the absence of a pharmacist may leave women feeling unsupported, which is important especially for young adolescents or first time users.

- **Provide advice on contraceptive alternatives**

The [redacted] website for pharmacists states the following: 'Pharmacists promote dialogue on contraceptive alternatives and influence the beliefs and the outcomes through effective counselling on EHCs. The supply of emergency contraception from pharmacies can be accompanied by patient education from pharmacists, who have expertise on this topic'.

Therefore, the consultation with a pharmacist is important for women to discuss their options. This may be important for women who have previously used [redacted] and have concerns about [redacted] e.g. its efficacy, side effects etc.

Assessor's comment: The absence of a pharmacists means a lost opportunity to discuss contraceptive options, and also long term contraception. Pharmacists are well placed to advise women on suitable methods of contraception, and also advise on the most effective form of emergency contraception, the copper coil. [redacted] stated that the GSL availability of [redacted] may result in a shift towards using the pill as a first line treatment for EC.

7 PROPOSED PRODUCT INFORMATION

7.1 Summary of Product Characteristics (SMPC)

The proposed SmPC is attached in Annex 7. The MAH has not proposed any changes to the SmPC. The MAH has specifically stated that the SmPC should reflect the state-of-the-art knowledge regarding a medicinal product and is primarily there to help healthcare professionals. They consider that as the change from P to GSL setting has no impact on the characteristics of the product, they propose to keep the current SmPC without implementing any change. They also consider that there will be a possibility of confusion if [redacted] emergency contraceptives remain on the market with the original SmPC, while the GSL version is different in a very important section such as contraindications.

The MAH has moved some of the warnings into the contraindications section in the leaflet and on the medicine box. However, in order for the leaflet and label to reflect the information in the SmPC, a section should have been included in section 4.4 which states 'The label will state…' to outline specifically what information will be included on the packaging.

7.2 Patient Information Leaflet (PIL)

The proposed PIL is attached in Annex 8.

The MAH have added some information on domestic violence, sexual assault and sexual abuse at the end of the leaflet. This includes an explanation of the different types of abuse, and the free helplines in England, Scotland and Wales where support is available. It also includes the helplines for anyone aged 16 and over who have experienced rape, sexual assault, sexual abuse or any other type of sexual violence. The helpline and website for Childline is also available for anyone under the age of 18 who requires support.
Finally, there is advice for anyone to call the police if they are in immediate danger.

Assessor's comment: The information included in the leaflet may be helpful to some people, however it is very unlikley to replace the role of a pharmacist in safeguarding this population. Pharmacists can provide instant support, share information appropriately with other healthcare professionals, and refer to relevant organisations. Therefore whilst there is information present in the leaflet, it does not guarantee that people will necessarily act to protect themselves. The duty of care in safeguarding the public cannot be replaced by the addition of this information in the leaflet.

Information in the leaflet has been reorganised to include some of the warnings as contraindications so that it is clear when [redacted] should not be taken. Some of these

changes still require further amendment, and if CHM advise in favour of the reclassification, these changes will be requested from the MAH.

7.3 Label

The proposed label is attached in Annex 9.

The label is not considered to be adequate to manage the risks associated with this product as a GSL medicine.

The MAH has stated that it was the experts' view that the risks associated with GSL availability of [redacted] could be effectively mitigated by the labelling. They considered that the proposed messages on the outer carton would be sufficient to enable consumers to make appropriate assessments about their own suitability for [redacted] and that the leaflet would provide the necessary additional information for users of [redacted] to enable them to use it effectively whilst also providing information about options for regular contraception, counselling about sexual health and signposting vulnerable women experiencing domestic violence and abuse to organisations that could provide help and support. The experts believed that these measures would be a very adequate substitute for the pharmacy consultation.

There are a number of inadequacies concerning the label which are outlined below:

- The information included about domestic violence and sexual abuse is not considered sufficient to manage the lost opportunity of safeguarding in a GSL setting.
- The label should list all interacting medicines which would not be suitable to take with [redacted] It is not acceptable to only include this information in the leaflet as an individual would need to know whether [redacted] is suitable to take <u>before</u> purchasing the medicine and having access to the leaflet.
- The MAH has proposed a [redacted]
- There is a considerable amount of text on the medicine box. The text is written exactly as stated in the leaflet and there is therefore scope to condense this.
- The key information is lost within the box, such as the indication and the dose. All essential information should be prominent.
- Some of the text, including the headings, are not user friendly, and should be written using more patient friendly language, e.g. 'speak to a doctor or pharmacist before taking [redacted] if' or 'what to do after taking [redacted] etc. The information should also be easy to navigate, so an individual would know where to look for certain information.

[redacted]

Label

Whilst not a regulatory requirement, the MAH was requested to conduct a readability test for the medicine box to ensure that potential users could locate, understand and appropriately act upon the information provided without the input of a healthcare professional. This is of particular importance for this application where there are both numerous and complex messages on the medicine box, and therefore evidence is required to demonstrate whether individuals could locate and understand important information without the presence of a pharmacist.

In total, the carton was tested on 23 members of the public; three during a pilot test, and the remaining 20 over two rounds of user testing. Each of these test participants was interviewed singly, face-to-face, by an experienced interviewer. Each participant was handed the carton, asked to read through it and then to answer, orally, a series of questions contained in a questionnaire. [redacted]

Results

In round 1, all questions were answered correctly. However, 10% (1 person out of 10) for questions 5, 7 and 9 found it difficult to find the information. These questions were:

Question 5: Imagine you are currently taking a hormonal contraception such as the pill, what effect might [redacted] have on your regular contraception?

Question 7: After you've taken this tablet your next period may be unusually light or heavy. What might this mean?

Question 9: If you vomit within 3 hours of taking the medicine, what should you do?

Of note, 3 participants stated that they liked the information on domestic abuse. One participant wanted information on what a woman should do if she was ovulating, and whether the medicine would work.

No changes were made to the carton after round one.

In round 2 all questions were answered correctly. However, 20% (2 people out of 10) found it difficult to find the information to question 4, and 10% (1 person out of 10) found it difficult to find the information to questions 7, 9, 10 and 12. Questions 7 and 9 are outlined above. Questions 4, 10 and 12 were:

Question 4: What age group can take this medicine?

Question 10: What does this leaflet say about your ability to get pregnant in future?

Question 12: What are the symptoms of an ectopic pregnancy?

Of note, 1 out of 10 participants considered the layout of the carton to be poor. 1 out of 10 participants also considered the information on the carton to be 'not very clear'. Also, 1 participant stated that they liked the information on sexual abuse, and 3 participants stated that they liked the peel flap.

Overall, no participants particularly struggled with the information on the carton. All found the language easy to understand and it could be seen that the bold headings were being used to aid navigation through the information. No incorrect answers or failures to locate information were seen in either phase of testing.

[redacted] Despite this, all participants were comfortable when handling the carton and searching the information.

Following the second round of user testing, no changes were recommended.

Assessor's comment:

Whilst all participants managed to locate and understand the information, some of the results are concerning.

Some participants found it difficult to locate important information, such as the course of action to take if they vomit after taking [redacted] This is an important point, particularly as this could affect the efficacy of the medicine. Any essential information, particularly aspects which could affect how the medicine works, should be very prominent and easy to locate.

Similarly, 2 out of the 10 participants in round 2 found it difficult to locate the age group that can take this medicine. This may suggest that the term [redacted]' may not be understood, and therefore this would need to be clarified. The target population is a basic yet essential aspect of the user testing, and it is expected that 100% of participants would be able to locate this with ease.

Another concerning point is that 1 participant in round 2 found it difficult to locate information related to the symptoms of pregnancy. These are symptoms which would require medical advice to be sought promptly, therefore it is imperative that these symptoms are clear and easy to find.

The concerning aspect of this user testing is that no questions were asked on the domestic violence/sexual abuse information that has been included. The safeguarding of vulnerable people is considered to be the most important aspect of this reclassification, therefore there is no evidence to demonstrate whether women can understand and can locate this.

The questions asked during the user testing covered most aspects of the label. However it would have been useful if the types of questions included scenario based questions to test whether women can understand when to take the medicine, whether they think it would be suitable to take, and when to seek medical advice.

The age range of women used in the user test is acceptable, however, it may have been useful to include one or two male participants, as the GSL availability of [redacted] would mean that anyone could purchase the medicine, which could include buying the medicine on behalf of someone.

Finally, one of the exclusion criteria for participants was 'not fluent to in speaking/reading English'. Women who do not speak or read English are very likely to be potential purchasers

of [redacted] as a GSL medicine, therefore for this application, it would be important to include this population.

8 RISK MANAGEMENT PLAN

This application is supported by a risk management plan (RMP) which identifies the important risks associated with the product and proposes how these will be managed in the product information (SmPC, labelling and patient information leaflet). In summary, it identifies the following ongoing safety concerns and provides what the MAH considers to be appropriate risk minimisation measures.

Important identified risks are risks that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant:
• Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk);
• Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk, or additional risk minimisation activities.

No identified risk was considered important for inclusion in the RMP.

Important potential risks to be included in the RMP are those risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Where there is a scientific rationale that an adverse clinical outcome might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product, the adverse reaction should be considered a potential risk, and if deemed important, should be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

The following are included as important potential risks- there are no changes to these risks compared to the P RMP.

- Effects on pregnancy maintenance/off label use – managed by SMPC, PIL and label
- Risk of incomplete abortion and heavy bleeding – managed by SMPC and PIL
- Effects on foetus and newborns – managed by SMPC and PIL
- Risk of ectopic pregnancy – managed by SMPC and PIL
- Concomitant use of CYP3A4 inducers – managed by SMPC, PIL and label
- Liver effects – no RMMs considered necessary
- Delayed menstrual period >60 days / amenorrhoea – managed by SMPC and PIL
- Ovarian cysts – managed by SMPC and PIL

Missing information relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

The following are included as missing information - there are no changes to these risks compared to the P RMP.

- Effect of concomitant use of progestin-containing contraception

- [redacted]
- Effects in women with impaired liver function

The MAH has provided an updated RMP as part of the application for the GSL reclassification. There are no additional risk minimisation measures proposed as part of this reclassification application. The MAH considers that the routine risk minimisation measures (product information) are considered sufficient to manage the risks associated with the availability of this product as a GSL medicine.

The below table is a summary of the important risks and the missing information.

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Effects on pregnancy maintenance/off label use • Risk of incomplete abortion and heavy bleeding • Effects on foetus and newborns • Risk of ectopic pregnancy • Concomitant use of CYP3A4 inducers • Liver effects • Delayed menstrual period >60 days / amenorrhoea • Ovarian cysts
Missing information	• Effect of concomitant use of progestin-containing contraception [redacted] • Effects in women with impaired liver function

Additional risk minimisation measures

[redacted]

[redacted]

Safeguarding

The lost opportunity for safeguarding is a significant risk associated with the reclassification of [redacted] to a GSL medicine.

The MAH was requested to include this risk in the RMP as it is considered that this could have an impact on the risk:benefit balance of the medicine. Instead the MAH have updated the RMP to include a section: 'SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP: additional potential risks associated with the reclassification from pharmacy-only (P) to General Sales List (GSL) with minimal clinical impact on patients.'

The risks included in this section consist of all risks outlined within the clinical overview which have been discussed throughout the paper. The MAH has stated that all of these potential risks related to reclassification from P to GSL supply were not considered relevant as additional safety concerns for inclusion in the RMP (except drug-drug interactions which is already listed in the RMP) because all were assessed as low or moderate by the expert panel who characterised the likelihood of occurrence of each risk in the GSL setting in comparison to the current P setting and clinical impact for the individual woman.

The RMP essentially states that well-trained pharmacists may be able to identify victims of domestic violence or abuse and ensure they are able to access the specialist services they need to escape and recover. However, they consider that encountering a woman in pharmacy who needed safeguarding was rare. Therefore, the MAH considers that the risk does not outweigh the benefit of having [redacted] available as GSL as the most important and immediate need of this group of women is to avoid an unplanned pregnancy. They have further stated that the availability of [redacted] as a GSL medicine does not mean that vulnerable women have no other recourse to get help.

The MAH have also reiterated in the RMP that they consider that the most important act of safeguarding for a vulnerable woman at immediate risk of pregnancy is to provide rapid and unfettered access to an effective emergency contraceptive, therefore avoiding unwanted pregnancy, which can pose a significant risk to a woman's health and wellbeing.

The MAH considers that the information on the medicine box and in the package leaflet is adequate to manage safeguarding in a GSL setting, as the wording encourages the woman to self-identify, or seek help to identify, and report abuse.

Assessor's comment: It is acknowledged that as a GSL medicine, there cannot be additional risk minimisation measures included as part of the risk management plan, as the medicine would be sold without any input from a healthcare professional such as a pharmacist.

However, based on the assessment against the GSL criterion, the routine risk minimisation measures, i.e. the label, is not considered sufficient to manage the risks associated with this medicine. Whilst not included in the RMP, the lost opportunity to safeguard vulnerable people is considered to be a major risk associated with this reclassification, and the information on the label is unlikley to manage this risk and replace the role of the pharmacist in the GSL setting.

9. DISCUSSION

General Sales List medicines are usually indicated for short term and easily identifiable conditions. These include small pack sizes of analgesics such as paracetamol and

ibuprofen, antihistamines, and cough and cold medicines. The risks associated with the supply of a GSL medicine should be minimal, and very easily managed through the information on the carton.

The suitability of [redacted] as a GSL medicine depends on the ability to adequately manage all risks associated with the medicine on the carton. Following the assessment of this application, it is not considered possible for the label to replace the role of the pharmacist in the supply of [redacted]

The role of the pharmacist in the supply of [redacted] is extensive. Pharmacists play a crucial role in ensuring [redacted] is only supplied if suitable and the appropriate advice is provided to increase the chance of the medicine being effective, e.g. advice related to the window of use, the action to take if vomiting is experienced, use with other medicines etc. In scenarios where [redacted] is not suitable, pharmacists are well-placed to provide an alternative treatment, e.g. [redacted] , or refer for the insertion of an intra-uterine device.

One essential role of a pharmacist is the safeguarding of vulnerable people. [redacted], or women who have been subject to domestic violence or sexual abuse. Pharmacists are trained to identify and help manage safeguarding concerns, which can include referral to appropriate services, sharing information with GPs when appropriate and parenteral intervention for children. The absence of a pharmacist, and as a consequence the lost opportunity of safeguarding the public, is the most significant concern associated with this reclassification.

As a GSL medicine, [redacted] could be used by [redacted] In particular, [redacted] could be potentially used by the following populations which would be classed as a significant safeguarding concern:

- [redacted]
- women [redacted] who are subject to domestic violence
- women [redacted] who are subject to sexual abuse or sexual violence

As a P medicine, the provision of EHC is usually carried out in a consultation room, which can allow pharmacists to determine whether there are any safeguarding issues. In particular, pharmacists can identify any signs of abuse, check for repeated use of EHC if the person has requested this frequently, and provide support if the individual appears anxious or afraid. The face to face interaction in the supply of [redacted] is considered essential in this aspect, as it would be virtually impossible to provide the same level of protection through the labelling. There is a risk, that in the absence of a pharmacist, some women or young adolescents may be less inclined or have a limited opportunity to raise their concern with a trusted healthcare professional.

The pharmacy organisations interviewed for this application highlighted the missed opportunity for safeguarding as one of their key objections to making [redacted] available as a GSL medicine. They also stated that encountering a woman in pharmacy who needed safeguarding was rare. Whilst it is difficult to establish the frequency of safeguarding concerns arising in a pharmacy, it would be highly inappropriate for a medicine to be available as GSL where there is a greater safeguarding risk than as P medicine.

Another major risk associated with this reclassification is the risk of unintentional misuse. Unlike other GSL medicines, the consequence of not using this medicine correctly is much

more significant, i.e. the possibility of a pregnancy. Pharmacists play a key role in ensuring that women are provided with the key advice to take the medicine effectively. The questions asked, often as part of a checklist, help to determine whether the [redacted] is suitable, and sometimes whether additional advice needs to be provided, e.g. advice related to concomitant medicines and ongoing contraception.

The availability of [redacted] as a GSL medicine could result in purchasing the medicine on behalf of someone else. There are two main concerns associated with this. Firstly, a woman being abused could ask a third party to purchase the medicine on their behalf. Whilst the MAH consider this to be a benefit, there is a risk that the safeguarding concern would go unnoticed and would continue. There is also a risk that the increased access could result in perpetrators continuing to abuse an individual as they are aware that EHC is more readily available. The second concern with purchasing on behalf of someone else is being unaware of any medical conditions/concomitant medications an individual may be taking, thereby resulting in use of [redacted] when it is not suitable, and which may not be effective. Currently, EHC is only provided to the individual requesting it, and often the service specification in a pharmacy requires a pharmacist to supervise intake to ensure that the medicine is not to be supplied to a third party.

There is a considerable risk that as a GSL medicine, individuals may self-select the medicine and take the tablet promptly without reading the label in detail. This is because most women requesting EHC are likely to be aware that the tablet needs to be taken as soon as possible. [redacted] mentioned that it is likely that after taking the pill, the medicine box may be thrown away. For [redacted] this is a particular concern, as the medicine box includes important advice and warnings to be aware of after taking the medicine. This includes advice on if the next period is late, advice if vomiting occurs, the symptoms of an ectopic pregnancy which would require medical advice to be sought etc. The risk of missing this information may result in an unintended pregnancy.

There are a number of medicines which should not be taken together with [redacted] as it could result in the reduced efficacy of the pill. The MAH has proposed including a broad reference to this on the label, e.g. ‘medicines for epilepsy, HIV tuberculosis, fungal infections’ etc. This is not acceptable and would not allow an individual to identify whether they are taking an interacting medicine. The absence of this specific information contributes to the risk of misuse, as without the clear information, women could take [redacted] when not suitable, which may result in the medicine being ineffective. At the same time, it is considered challenging to include all essential information on the label without it being cumbersome and illegible.

The MAH considers that the benefits of GSL availability of [redacted] include improved access due to restricted pharmacy opening hours. However there is already considerable access as many pharmacies are open during the weekends and bank holidays, and many are open until late in the evening. This benefit does not outweigh the risks associated with this reclassification.

They have further stated that there is a lack of availability of trained pharmacists when EHC is required. Most pharmacies offer EHC, and whilst pharmacies may be busy, pharmacists are usually available to offer this service. In the unlikley event that a pharmacist was not able to provide EHC, there are other pharmacies and other clinics that would be open and available to provide it.

The MAH is concerned that the current request for EHC from a pharmacy can be embarrassing and may infringe on an individual’s privacy. This is understandable, however

the precautions to safeguard women, ascertain whether the medicine is suitable for them, and provide clear advice on the use of the medicine outweighs this concern. Pharmacists are very likely to utilise the consultation room to go through a checklist of questions before supplying EHC so that the conversation can take place privately.

The MAH considers that the importance of accessing EHC as soon as possible following UPSI is to maximise the effectiveness of it, thereby reducing the number of unwanted pregnancies. Whilst the GSL availability of [redacted] would significantly improve access to the medicine, there may not be a direct reduction in the number of pregnancies. This is because for [redacted] to be effective, the medicine must be taken appropriately in accordance with the information on the medicine box. This includes instructions and advice both before and after taking [redacted] for example the need to check for a pregnancy after taking the medicine. There is a risk that if the medicine is taken without reading the information on the box, or if the information is not followed carefully, [redacted] may not be effective, which could actually result in an unintended pregnancy.

The GSL criterion has not been met as there is considered to be a hazard to health if the medicine is not used correctly. The increased access to the medicine and the requirement to take the medicine within a short timeframe is likely to contribute to taking the medicine immediately without reading the medicine box in detail. [redacted] There is also a significant risk of misuse associated with the GSL availability of [redacted]. The most important concern is the lost opportunity of safeguarding vulnerable populations, and the duty of care in safeguarding the public cannot be replaced by the addition of information in the leaflet and on the label.

To conclude, it is considered impossible to replace the role of a pharmacist in the supply of [redacted] with information on the medicine box.

10. CONCLUSION

It is considered that [redacted] containing [redacted] cannot be supplied safely without the supervision of a pharmacist.

The major issues associated with this application are outlined below:

- The GSL availability would result in a lost opportunity to safeguard vulnerable women, such as those under 16 and/or those subject to domestic violence or sexual abuse. The duty of care in safeguarding the public cannot be replaced by the addition of information in the leaflet and on the label.
- There are both numerous and complex messages to include on the label, and if these are not adhered to the efficacy of the product would be reduced, and possibly result in additional unintended pregnancies. Due to the nature of this medicine, in that most women are aware it needs to be taken as soon as possible, it is considered likely that key information would not either be read and/or followed and/or understood in a GSL setting.

This reclassification is not recommended for approval.

11. ADVICE SOUGHT

The EAG's advice is sought on whether they agree that [redacted] containing [redacted], cannot be approved as a general sales list medicine.

12. LIST OF ANNEXES

[redacted]