GEDEON RICHTER PLC.

EU RISK MANGAMENT PLAN

FOR

FYLREVY

(estetrol 14.2 mg and 18.9 mg film coated tablets)

EU Risk Management Plan for FYLREVY (estetrol 14.2 mg and 18.9 mg)

RMP version to be assessed as part of this application:	
RMP Version number:	0.4
Data lock point for this RMP:	24 September 2025
Date of final sign off:	See e-signature page at the end of document
Rationale for submitting an updated RMP:	Not applicable
Summary of significant changes in this RMP:	Not applicable
Other RMP versions under evaluation:	
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

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[redacted]

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List of Abbreviations

ATC	Anatomical Therapeutic Chemical code
ATE	Arterial thromboembolism
eCTD	electronic common technical document
E2	17β-oestradiol
E4	Estetrol monohydrate
EEA	European economic area
EMAS	European Menopause and Andropause Society
ER	Oestrogen receptor
HRT	Hormone replacement therapy
NAMS	North American Menopause Society
NK3	Neurokinin 3
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
P4	Progesterone
PIL	Product information leaflet
SmPC	Summary of Product Characteristics
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
VVA	Vulvovaginal atrophy

Part I: Product(s) Overview

Table 1: Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Estetrol
Pharmacotherapeutic group(s) (ATC Code)	Sex hormones and modulators of the genital system, natural and semisynthetic oestrogens, plain ATC code: G03CA10
Marketing Authorisation Applicant	Gedeon Richter Plc
Medicinal products to which this RMP refers	Two
Invented name(s) in the European Economic Area (EEA)	FYLREVY
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Sex hormones and modulators of the genital system, natural and semisynthetic oestrogens, plain. Estetrol is a natural oestrogen which is produced by the human foetal liver during pregnancy.
	Summary of mode of action: Estetrol substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms, including vasomotor symptoms.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	link to SmPC, PIL on EMA website
Indication(s) in the EEA	Current: Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in hysterectomised postmenopausal women Hormone replacement therapy for oestrogen deficiency symptoms in non-hysterectomised postmenopausal women with at least 12 months since last menses.
	Proposed: Not applicable
Dosage in the EEA	Current: One tablet is to be taken daily for each 28-day pack (28 consecutive days followed by the subsequent pack).

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Each film-coated tablet contains 14.2 mg estetrol (as 15 mg estetrol monohydrate) or 18.9 mg estetrol (as 20 mg estetrol monohydrate).
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

A hormone replacement therapy (HRT) for oestrogen deficiency symptoms in hysterectomised post-menopausal women and in non-hysterectomised postmenopausal women with at least 12 months since last menses.

Prevalence:

Vasomotor symptoms (VMS) are the most common and bothersome menopausal complaint and occur most often in the late menopausal transition and the early post-menopause. Up to 80% of menopausal women suffer from VMS, which last a mean duration of 7 to 9 years. In one-third of women, VMS can last more than 10 years (NAMS, 2023).

Demographics of the population in the proposed indication:

FYLREVY is indicated as HRT in hysterectomised post-menopausal women and non-hysterectomised post-menopausal women with at least 12 months since last menses who are seeking relief of oestrogen deficiency symptoms such as VMS. The safety and efficacy of FYLREVY have been established in this population of post-menopausal women exhibiting symptoms of oestrogen deficiency.

The main existing treatment options:

There are a variety of treatment options for oestrogen deficiency symptoms in post-menopausal women which vary widely depending on their effectiveness and the severity of the symptoms. The gold standard treatment, especially for moderate to severe symptoms is HRT, however, more than two-thirds of postmenopausal women seeking treatment are not treated with HRT (Nappi et al., 2023). The other frequently used therapies for the relief of oestrogen deficiency symptoms are non-hormonal treatment requiring a prescription, over the counter treatments and lifestyle changes; treatment options are often combined to relieve symptoms (REALISE study, Kingsberg et al., 2024). The following rates were observed for the treatment of moderate to severe symptoms (REALISE study, Kingsberg et al., 2024):

- Hormonal therapy (49.8%) – e.g. oestradiol, progesterone, conjugated equine oestrogens
- Non-hormonal therapy:
    - Selective serotonin reuptake inhibitor (SSRIs)/ Serotonin-norepinephrine reuptake inhibitor (SNRIs) (15.7%) – venlafaxine, paroxetine, citalopram
    - Other therapy (16.6%) – tibolone, raloxifene, gabapentin
- Lifestyle changes (78.3%°) – increased exercise, eating a balanced, rest and relaxation
- Over the counter treatments (57.6%) – calcium/vitamin D, black cohosh, soy products

HRT may contain oestrogen alone or an oestrogen and a progestogen (taken continuously or sequentially for 14 days). The choice of combining therapy with a progestogen is dependent on the presence of an intact uterus.

Oestrogens proposed in HRT are available as oral conjugated equine oestrogens, synthetic ethinylestradiol, micronized oestradiol and oestradiol valerate. Oestradiol therapy can also be prescribed as a transdermal patch, as a daily gel or skin spray or as a slow-release subcutaneous implant. The availability of the different forms varies between countries, the most widely prescribed oestrogen formulations being oral preparations (Davis and Barber, 2022). Non-hormonal alternative treatments have emerged over the last 20 years. Those treatments are mainly SSRIs such as paroxetine, citalopram or escitalopram and SNRIs such as venlafaxine or desvenlafaxine, and the recently approved (neurokinin) NK3 receptor antagonist fezolinetant. In Europe, SSRIs and SNRIs are not approved for the indication of the treatment of VMS and their use is therefore off-label. According to international guidelines, these non-hormonal alternatives should be considered as a second-line treatment and offered to women who cannot use HRT because of contraindications or personal preference (Rees et al., 2022). SSRIs and SNRIs only target VMS, do not improve VVA and have no effect on bone mass loss associated with menopause.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In addition to VMS such as hot flushes, post-menopausal women may experience night sweats, and symptoms of vulvovaginal atrophy (VVA), which are part of the genitourinary syndrome of menopause (Portman and Gass, 2014). These symptoms include vaginal dryness, itching, dyspareunia and urinary tract problems. VVA may occur in 50-70% of post-menopausal women, can negatively impact quality of life, and tends to worsen with age (Aninye et al., 2021).

Other menopausal symptoms include mood changes such as depression and anxiety, sleep and cognitive disturbances such as insomnia, fatigue, irritability and difficulties with short-term memory and concentration, as well as muscle and joint discomfort (El Khoudary et al., 2020) and the EMAS European Menopause and Andropause Society (EMAS) position statement (Rees et al., 2022). The incidence of sleep disturbances in the menopausal transition ranges from 16% to 47% at peri-menopause (transitional period preceding menopause, during which levels of oestrogens start decreasing and menopausal symptoms may appear) and 35% to 60% at post-menopause (Tandon et al., 2022). VMS have been shown to act as a key component of sleep disruption during peri- and post-menopause (Baker et al., 2018). Sleep disturbances may have a deep impact on the women's QoL, work productivity, and healthcare utilization and can have long-term effects on health and wellbeing across several years of the menopausal transition (Bolge et al., 2010).

Post-menopausal women also have an increased risk of osteoporosis due to the oestrogen deficiency which may be presented by up to 50% of women by the age of 80 years (Panay et al., 2024). Osteoporosis increases the risk of fractures, which occur most frequently in the spine, hip and wrist in post-menopausal women with osteoporosis (van Staa et al., 2001), and might lead to long-term disability. Bone health is known to be correlated with biomarkers measurable in the blood. An increase in the levels of bone turnover biomarkers after menopause, associated with higher rates of bone loss, has been documented consistently through the literature (Rogers and Eastell, 2000; Reginster et al., 2001).

Important co-morbidities:

Post-menopausal women may be at increased risk of serious health conditions. These conditions include:

- Cardiovascular disease, such as venous thromboembolism (VTE) and arterial thromboembolism (ATE)
- Hypertension
- Diabetes
- Dyslipidaemia
- Metabolic syndrome
- Osteoporosis

Research is ongoing into the contribution of hormone changes to most of these conditions (Aninye et al., 2021).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Table 2: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single- and repeat-dose toxicity studies **Estetrol alone** E4 displayed low acute oral toxicity: a single oral dose of 1000 mg/kg was well tolerated in female Sprague-Dawley rats and in female cynomolgus monkeys (ES-T09, ES-T05). Repeat-dose oral toxicity studies with E4 were performed up to 26 weeks in female Sprague-Dawley rats and up to 39 weeks in female cynomolgus monkeys. Studies were conducted in female CD-1 mice and in female Wistar rats up to 13 weeks to establish suitable dose levels for the carcinogenicity studies in the same species and strains. E4 was administered to female mice at dose levels up to 30 mg/kg/day, to female rats at dose levels up to 150 (Sprague-Dawley) or 6 (Wistar) mg/kg/day and to female monkeys at dose levels up to 50 mg/kg/day (ES-T31, ES-T34, ES-T40, ES-T09, ES-T10, ES-T18, ES-T39, ES-T11, ES-T15, ES-T20). No treatment-related mortality occurred. Mice displayed a dose-related increase in body weight gain, and rats and monkeys a dose-related decrease of body weight gain or body weight loss. Changes in body weight gain were accompanied by changes in food consumption. Reduced body weight gain is commonly observed with oestrogens in rat and monkey and has also been reported in mice although an initially enhanced body weight gain may occur in the latter species. Treatment-related clinical signs in rat and monkey included alopecia and thin appearance. Atrophy of hair follicles and/or empty hair follicles were found microscopically in skin of both species and this finding was not considered to be adverse.	*Weight changes* Species-specific changes in weight in mice, rat and monkey. Weight was monitored during the clinical development program with an increase in weight noted in the MIT-Do001-C302 study in a greater number of women without an intact uterus. The weight increase was not dose dependent and not clinically relevant. *Alopecia* Alopecia and thinning hair were observed in rat and monkey but not identified in the clinical development program. *Haemostasis parameters, proteins, lipids and liver enzymes* No clinically relevant impact on haemostasis parameters was observed in the clinical development program.

Key safety findings (from non-clinical studies)	Relevance to human usage
Minimal to moderate increases in clotting times (notably prothrombin time) were noted in rat. Several serum chemistry parameters displayed minimal to moderate treatment-related changes. These included changes in protein and albumin (increase in rat, decrease in monkey), cholesterol (decrease in rat, increase in monkey), triglycerides (increase in all species), alkaline phosphatase (increase in mouse and rat, decrease in monkey), alanine aminotransferase (increase in monkey) and γ-glutamyl transferase (decrease in monkey). Liver weight increased in mouse and rat. Microscopic changes in liver included minimal to moderate hepatocellular hypertrophy in mouse and rat, minimal to moderate hepatocellular microvacuolation in rat, and a decreased glycogen content in monkey. In the absence of microscopic degenerative changes, the findings were not considered to be adverse. Further serum chemistry parameters displaying minimal to moderate treatment-related changes included inorganic phosphorus (increase in mouse and rat), urea (decrease in mouse), and creatinine (decrease in mouse and rat). Minimal to moderate brown pigment deposition (lipofuscin or hemosiderin) and minimal to slight tubular dilation/tubular cell vacuolation were observed in rat kidney. In the absence of microscopic degenerative changes in kidney, the findings were not considered to be adverse. Mouse and rat showed an increase in trabeculae in femoral bone which was consistent with the oestrogenic properties of E4 (Tobias et al, 1991) and not considered to be adverse. Observed effects in the repeat-dose toxicity studies were explained by the pharmacological properties of E4 and NOAELs were mainly determined by reduced body weight (gain). NOAELs in the chronic repeat-dose studies were 5 mg/kg/day in rats and 3 mg/kg/day in monkeys. $AUC_{0\text{-last}}$ and C_{max} at these dose levels were 736 ng·hr/mL and 238 ng/mL in rats and 328 ng·hr/mL and 97.2 ng/mL in monkeys at the end of treatment. **Estetrol in combination with progesterone** E4 was evaluated in combination with P4 at dose levels up to E4/P4 10/100 mg/kg/day in a 13-week toxicity study in female cynomolgus monkeys (Do001-NC-01) to support the conduct of the HRT clinical program. Minimal to mild changes in clinical pathology parameters (*i.e.,* decreased red blood cell counts, haematocrit and haemoglobin concentrations, shortened prothrombin	*Estetrol in combination with progesterone* Haematology and liver function were monitored during the clinical development program including in the MIT-Do001-C302 SSP in which women with an intact uterus were treated with E4 20 mg and continuous P4 100 mg. No clinically relevant effect of the treatment on haematology and liver function parameters was observed.

Key safety findings (from non-clinical studies)	Relevance to human usage
time, decreased total protein and albumin levels, decrease in gamma-glutamyl transferase and alkaline phosphatase) were observed in the animals treated with E4 alone as well as in the animals treated with the combination E4/P4, at all dose levels in a dose-related manner. In animals treated with E4 alone, an increase in cholesterol concentration was noted as well. These findings were non-adverse and reversible (at least partially). Minimal to mild changes in clinical pathology parameters (*i.e.*, decreased red blood cell counts, haematocrit and haemoglobin concentrations, shortened prothrombin time, decreased total protein and albumin levels, decrease in gamma-glutamyl transferase and alkaline phosphatase) were observed in the animals treated with E4 alone as well as in the animals treated with the combination E4/P4, at all dose levels in a dose-related manner. In animals treated with E4 alone, an increase in cholesterol concentration was noted as well. These findings were non-adverse and reversible (at least partially). At histopathological examination, non-adverse effects, related to the pharmacological activity of the compounds, were observed in the female genital organs (ovaries, uterus, cervix, vagina, oviducts) and mammary gland at all dose levels of the combination and with E4 or P4 alone. In addition, changes reflecting the pharmacological activity of the compounds were noted in the pituitary gland in groups treated with E4 alone and the combination. Effects with the combination were observed in all these organs showing a dose relationship in incidence and/or severity. At the end of the treatment-free period, partial recovery was observed in the pituitary gland, uterus, ovaries, thymus, and skin.	
Reproductive/developmental toxicity In return-to-fertility studies with E4 in female Wistar rats, dose-related reduced body weight gain and food consumption were noted during the 4-week treatment period at oral dose levels up to 1.5 mg/kg/day. An increase in the number of non-cycling females (0.5 and 1.5 mg/kg/day) was found as well as an increase in the number of cycles lasting 3 days or more (1.5 mg/kg/day). Body weight and food consumption showed partial to complete recovery during the 3-week post-dose treatment-free period and estrus cycle recovery was complete within the first week after cessation of treatment. There was no effect on mating, fertility or gestation indices, and there was no effect on implantation data. The studies provide clear evidence for a return-of-fertility after cessation of treatment. The NOAEL was	E4 is indicated for use in post-menopausal women in whom pregnancy should not occur.

Key safety findings (from non-clinical studies)	Relevance to human usage
0.17 mg/kg/day for estrus cycling. The NOEL for fertility and early embryonic development was 1.5 mg/kg/day. Exposures were not determined (ES-T27, ES-T43). An early embryonic development study in rats dosing from gestation day 0 (G0) to G6 was not performed. Such a study was not considered useful, because E4 was found to completely inhibit implantation at oral dose levels ≥ 0.1 mg/kg/day *bid* in a non-GLP study in New Zealand White rabbits dosed from 4 days prior to mating until G9. E4 treatment caused abortion and/or total litter loss at 3 mg/kg/day in rat and at 0.15 and 0.45 mg/kg/day in rabbit, leading to several premature sacrifices in both species. Reduction of the treatment period at 0.45 mg/kg/day did not improve pregnancy outcome in rabbits. Foetal evaluations in rabbits were based on the 0.05 and 0.15 mg/kg/day dose groups, since there were only two litters at 0.45 mg/kg/day. Both species displayed maternal toxicity at all dose levels, as indicated by reduced body weight gain and food consumption. In addition, clinical signs (areas of hair loss, emaciated appearance, absence of faeces) were recorded in rabbits at 0.15 and/or 0.45 mg/kg/day. Large or thick placentas were noted at necropsy in rats at 1 and 3 mg/kg/day. In females with live foetuses, post-implantation loss was enhanced at the highest dose level in both species but there was no effect on pre-implantation loss, the number of live foetuses or foetal sex ratio. Foetal developmental delays were observed in both species. In rats, these consisted of incomplete/non-ossification of the sternebrae and increases in nodulated and kinked ribs at 1 and 3 mg/kg/day, and a reduction of foetal weight at 3 mg/kg/day. Foetal developmental delays in rabbits included supernumerary 13th ribs at 0.05 and 0.15 mg/kg/day, and incomplete/non-ossification of phalanges, several bones, and vertebral centra at 0.15 mg/kg/day. The embryolethal effects and foetal growth retardation noted at dose levels associated with maternal toxicity in both species evaluated are typical effects of exogenous oestrogens, which have been described to interfere with pregnancy when given to rats and rabbits and to cause embryonic mortality/abortion and delay of foetal growth in those species (Dreisbach et al, 1959; Haddad and Ketchel 1969; Bartholomeusz et al, 1999; IARC, 1999).	

Key safety findings (from non-clinical studies)	Relevance to human usage
There were no treatment-related malformations in rabbits. In rats, shortening, thickening or bending of long bones (humerus, radius) and scapula were found in 3 foetuses from 3 litters at E4 1 mg/kg/day and in 5 foetuses from 4 litters at E4 3 mg/kg/day. Several foetuses also had malrotated and severely flexed ankle joints. The observed skeletal anomalies were classified and reported as malformations. However, several publications on foetal skeletal findings in the Han Wistar rat (the strain used in the study with E4) support that these skeletal anomalies are transient and reversible variations since they are described to remodel after birth and resolve at weaning (Mitchard & Stewart, 2014; Kimmel et al, 2014; de Schaepdrijver et al, 2014). These skeletal anomalies are generally secondary to maternal toxicity and are thought to reflect the short gestation period in rats with their 'repair' due to the increase in bone mass and remodelling that occurs postnatally (Expert report Clode 2018). The background incidence of the mentioned skeletal observations in Han Wistar rats appears to be variable over time (Mitchard & Stewart, 2014). Kimmel et al. (2014) evaluated a large number of published embryo-foetal development studies and concluded that bent/short long bones and bent scapula frequently occur (although at a usually lower incidence) together with wavy ribs under conditions associated with maternal and/or foetal toxicity, and that these changes are transient and should be classified as variations rather than malformations unless external observation of the limb indicates shortening and/or malformation. In the rat study with E4, maternal toxicity and foetal toxicity or developmental delays were noted at both 1 and 3 mg/kg/day E4. All individual animals displaying bent/short-long bones and/or bent scapula also had nodulated and/or kinked ribs and the overall percentage of foetuses with nodulated/kinked ribs was higher than the percentage of foetuses with affected long bones and/or scapula. Only one (particularly affected) foetus at 1 mg/kg/day had severely shortened fore- and hindlimbs upon external observation. The observed skeletal anomalies in the rat are concluded to be of the transient nature as described by Kimmel et al. (2014). Regarding the external observations (joint flexures), administration of exogenous oestrogens modifies the uterine environment by increasing contractions in the pregnant uterus in late pregnancy. Increased uterine tone associated with enlarged placenta induced by oestrogens participates to reduce the uterine space, leading to subsequent abnormal foetal compression. This is supported by the co-existence of	

Key safety findings (from non-clinical studies)	Relevance to human usage
multiple observations in same litters. The inconsistency in the directional nature of the flexures also supports that there is no specific teratogenic event during organogenesis affecting the original formation of the bones of the limbs. DeSesso and Sciallia (2018) describes the reversibility of this type of deformations. The external and skeletal observations (short/bent bones and joint flexures) observed in the rat are concluded to be part of an overall spectrum of deformations related to oestrogenic influence in the rodent and capable of recovery postnatally. Moreover, in the pre-/postnatal development study in rats at doses up to 1.5 mg/kg/day (Es0001-NC-003; TS Table 2.6.7.14), there were no indications of irreversible anomalies in live off-spring. These observations in rat are therefore not considered to point to intrinsic teratogenic properties of E4. Based on the spectrum of changes induced by the pharmacological activity (oestrogenic) of E4 and on the capacity of reversibility of the skeletal/external anomalies and given the embryolethal effects at E4 3 mg/kg/day, the NOAEL for embryo-foetal development in rats is concluded to be 1 mg/kg/day. $AUC_{0\text{-last}}$ and C_{max} after repeated dosing at 1 mg/kg/day were 37.7 ng·hr/mL and 20.9 ng/mL, respectively. The NOAEL in rabbits for maternal reproductive parameters and embryo-foetal development was 0.05 mg/kg/day, associated with an $AUC_{0\text{-last}}$ of 6.84 ng·hr/mL and a C_{max} of 0.925 ng/mL at the end of treatment. In a pre-/postnatal development study in pregnant female rats, several F_0 females treated at oral dose levels of 0.5 or 1.5 mg/kg/day were found dead or sacrificed prematurely for reasons of parturition difficulties, evident as “found dead” litter or absence of delivery. Multiple clinical signs were noted at 1.5 mg/kg/day, mostly in females sacrificed prematurely, and reddish vaginal discharge was recorded at both dose levels. At both dose levels, F_0 females also displayed reduced body weight gain and food consumption during pregnancy and/or lactation. At 0.5 mg/kg/day, one entire F_0 litter died on Day 2 *post partum* (*pp)* and increased incidences of cannibalized and “found dead” pups resulted in a reduced viability index on Day 4 *pp* at 1.5 mg/kg/day. There were no other noteworthy observations in F_0, nor in F_1 animals with the exception of a slight non-adverse reduced body weight gain and food consumption in F_1 males at 0.5 and 1.5 mg/kg/day. The majority of observations in the pre-/postnatal study can be attributed to parturition difficulties and/or abnormal maternal behaviour resulting from those parturition difficulties. The NOAELs for gestation and lactation in F_0 females	

Key safety findings (from non-clinical studies)	Relevance to human usage
were considered to be 0.5 and 0.17 mg/kg/day, respectively. The NOAEL for F_0 pups Day 4 *pp* viability was 0.17 mg/kg/day, and the NOEL for survival after Day 4 *pp* and the development of F_0 pups was 1.5 mg/kg/day. The NOAEL for the development, reproductive performance and fertility of the F_1 generation was 1.5 mg/kg/day (Es0001-NC-001, Es0001-NC-009, Es0001-NC-003). Administration of oestrogens in pregnant rodents disturbs uterine activity and impacts parturition, including gestational duration (Yanagimachi et al, 1968; Kraus et al, 1993; Murakami, 2016). Infanticide as a result of oestrogen administration has been observed in C57BL female mice (Mann et al, 1983). An experimental simulation of neuroendocrine dynamics at periparturient periods by programmed infusion of E2 in rats resulted a high incidence of stillbirth and lack of lactation, difficulties in labour and cannibalism (Inoue, 1981). In addition, parturition difficulties in rats have also been reported for selective oestrogen receptor modulators including dose-dependent reduction of maternal body weight, an increase of gestation duration, and delayed, prolonged or problematic parturition, resulting in maternal mortality/morbidity and enhanced numbers of dead pups (Buelke-Sam et al, 1998a, Buelke-Sam et al, 1998b, Weisenburger et al, 2004).	
Genotoxicity Genotoxicity tests with E4 were performed in: - Ames test in *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA, E4 was not mutagenic at concentrations up to the limit concentration of 5000 µg/plate ((ICH S2(R1)), in the absence or presence of metabolic activation. In *Salmonella typhimurium* strain TA102, increase in revertant colonies was noted both in the absence and presence of metabolic activation in two studies but not in a third study conducted at a different laboratory (ES-T21, ES-T29, ES-T48). - First mouse lymphoma assay, E4 produced increases in mutant frequencies in the presence of metabolic activation which exceeded the Global Evaluation Factor threshold (126×10^{-6}) at concentrations of 875 and/or 1000 µg/mL. in a follow up mouse lymphoma assay, E4 did not induce gene mutations in either the absence or presence of metabolic activation at non-precipitating concentrations up to the limit concentration of 1 mM (304 µg/mL) (ICH S2(R1)) (ES-T22, ES-T45)	Genotoxicity tests in mice and rats provided no clinically relevant information which required monitoring during the clinical development program.

Key safety findings (from non-clinical studies)	Relevance to human usage
- *In vivo*, bone marrow micronucleus test in female Sprague-Dawley rats at single oral dose levels up to the limit dose of 2000 mg/kg (ICH S2(R1)), associated with average plasma levels of 42.4 µg/mL at the approximate T_{max} (0.5 hour) E4 was negative (ES-T37). - Comet assay in female Sprague-Dawley rats in view of E4 findings in Ames test in *Salmonella typhimurium* strain TA102. E4 did not induce an increase of median tail intensity (% DNA in tail) in rat liver in either study at oral dose levels up to the limit dose of 2000 mg/kg/day (ICH S2(R1)). In second Comet assay, considered more robust, E4 induced no DNA damage or cytotoxicity in duodenum up to and including the limit dose of 2000 mg/kg/day. Plasma concentrations of E4 at 2000 mg/kg averaged 22.8 µg/mL at 0.5 hour in this study (ES-T46, 0030-NC-001). While E4 showed some indications of a weak genotoxic potential in vitro, there was no convincing evidence of genotoxic activity at high doses (2000 mg/kg) in vivo. At the approximate T_{max} (0.5 hour), average plasma concentrations of E4 were between 22.8 and 42.4 µg/mL at this dose level.	
Carcinogenicity Two-year carcinogenicity studies with E4 were conducted at oral dose levels of 0, 0.125, 0.25, 0.5 and 1 mg/kg/day in female CD-1 mice and 0, 0.08, 0.27 and 0.8 mg/kg/day in female Wistar rats. In mice, the Maximum Tolerated Dose (MTD) was considered to be achieved, based on increased body weight gain (+15% at 0.5 and +33% at 1 mg/kg/day) and enhanced body weights at notably 1 mg/kg/day during the first 3 months of treatment. E4 caused an increase in epithelial and stromal neoplasms in uterine and cervix at dose levels ≥ 0.25 mg/kg/day, in mammary gland neoplasms (adenoma, adenocarcinoma, benign and malignant adenoacanthoma) and in pituitary gland neoplasms (adenoma and carcinoma in pars distalis) at 1 mg/kg/day. Although there was no treatment effect on overall survival, mortality due to mammary neoplasms and to uterine/vaginal prolapse (caused by the presence of uterine and/or cervical neoplasms) was enhanced at dose levels ≥ 0.25 mg/kg/day. Increases in non-neoplastic proliferative findings were found in uterus (adenomyosis, cystic glandular hyperplasia) and mammary glands (acinar cell and atypical hyperplasia) at all dose levels, and in pituitary gland (hyperplasia in pars distalis) and lungs (broncho-alveolar hyperplasia) at 1 mg/kg/day.	E4 has a lower potency than E2 for stimulation of breast cancer cell proliferation, migration and invasion, and attenuates the effects induced by E2 (PR3032, PR3101). E4 inhibits tumour development in the DMBA-rat mammary tumour model, in contrast to EE at equipotent (i.e. 20-fold lower) doses. At high doses, E4 also causes regression of existing tumours in this model (PR3028, PR3049, PR3066). A cancer risk, however, cannot be entirely excluded. The SmPC for E4 contraindicates the use in women with known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer) and warns there is an increased risk of breast cancer in women taking combined oestrogen-progestagen or oestrogen-only HRT, which is dependent on the duration of taking HRT.

Key safety findings (from non-clinical studies)	Relevance to human usage
Treatment-related clinical pathology and non-proliferative observations (in uterus, vagina, mammary glands, pituitary gland, thyroid and adrenal glands, liver, stomach, sternum/femur, brain and spleen) were consistent with the oestrogenic properties of E4, secondary to other findings and/or of limited toxicological importance (Greaves, 2012) (0031-NC-004). In rats, the MTD was considered to be achieved, based on decreased body weight gain (≥ 10% at 0.27 and 0.8 mg/kg/day during the first 12 – 18 months and close to 10% during the entire treatment period). An increased incidence of mammary gland neoplasms (adenocarcinoma) was noted at a dose of 0.8 mg/kg/day. Increases in non-neoplastic proliferative findings were observed in the same tissue (acinar cell hyperplasia) at all dose levels, and in uterus (cystic glandular and atypical hyperplasia) and liver (clear cell foci containing glycogen) at dose levels ≥ 0.27 mg/kg/day. Proliferative findings in ovaries (interstitial cell hyperplasia) and incidence/severity of basophilic cell foci in liver showed a decrease in E4-treated groups compared to controls. Treatment-related clinical pathology and non-proliferative observations (in uterus, vagina, ovaries, adrenal glands, liver, brain, thymus, mesenteric lymph nodes, and spleen) in rats were consistent with the oestrogenic properties of E4, secondary to other findings and/or commonly observed in ageing animals (Greaves, 2012; Laast et al, 2014; McInnes et al, 2011; Pearse et al, 2006) (0031-NC-003). E4 was considered to be carcinogenic in mice at oral dose levels ≥ 0.25 mg/kg/day and in rats at an oral dose of 0.8 mg/kg/day. In mice, the dose level of 0.125 mg/kg/day was not carcinogenic. This dose level was associated with an $AUC_{0\text{-last}}$ of 4.60 ng·hr/mL and a C_{max} of 3.75 ng/mL in Week 25. In rats, the dose level of 0.27 mg/kg/day was not carcinogenic. This dose level was associated with an $AUC_{0\text{-last}}$ of 18.8 ng·hr/mL and a C_{max} of 9.99 ng/mL in Week 25. The observed neoplastic and non-neoplastic proliferative findings with E4 in mammary glands, uterus/cervix and pituitary gland in mice and in mammary glands in rats are consistent with those reported for other oestrogens such as EE and mestranol in those species. Overall, the observed neoplastic and non-neoplastic proliferative findings with E4 in mice and rats are consistent with its oestrogenic properties.	

Key safety findings (from non-clinical studies)	Relevance to human usage
Safety pharmacology	
Central nervous system E4 showed no effects in a Functional Observation Battery in conscious female Sprague-Dawley rats up to and including a single oral dose of 15 mg/kg. **Cardiovascular system** E4 had no effect on heart rate, blood pressure or electrocardiogram parameters and did not induce arrhythmia in conscious telemetered female cynomolgus monkeys, at single oral dose levels up to and including the highest tested dose of 100 mg/kg (ES-T23). **Respiratory system** E4 did not affect respiratory parameters in conscious female Sprague-Dawley rats at single oral dose levels up to and including the highest tested dose of 150 mg/kg (ES-T24).	The safety pharmacology studies revealed no relevant effects or cause for concern on cardiovascular, respiratory or central nervous systems.

Table 3: Conclusions on non-clinical data

Safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part II: Module SIII - Clinical trial exposure

The total exposure to E4 in the completed clinical trials was 2 903 subjects (2 759 women and 144 men) including 2 558 female subjects exposed to 15 mg dose or above. Details of exposure in female subjects by duration, age and ethnicity are provided below.

Table 4: SIII.1: Subject number by duration of exposure and dose

Duration of exposure	0.1 mg	1 mg	2 mg	2.5 mg	5 mg	10 mg	15 mg	20 mg	28.3 mg IV	30 mg	40 mg	45 mg	60 mg	100 mg	Total
≥ 1 day	6	6	10	52	56	80	544	1944[a]	3	28	12	16	3	38	**2759**[b]
≥ 28 days	0	0	0	49	45	62	436	1702	0	0	3	0	3	0	**2300**
≥ 84 days	0	0	0	41	39	35	364	1354	0	0	3	0	3	0	**1839**
≥ 365 days	0	0	0	0	0	0	91	511	0	0	0	0	0	0	**602**

[a] including 922 subjects with continuous use of progesterone 100 mg, [b] 39 subjects were exposed to different doses due to the crossover (MIT-Do001-C104) and two period (MIT-Es0001-C102) design

Table 5: SIII.2: Subject exposure by age and dose for E4 15 and 20 mg

Age	15 mg	20 mg
< 50	102	325
≥ 50 < 65	409	1579
≥ 65 < 75	26	35
≥ 75 < 85	6	0
≥ 85	1	0
Unknown	0	5
Total	**544**	**1944**

Table 6: SIII.4: Subject exposure by race and dose for E4 15 and 20 mg

Race	E4 15 mg	E4 20 mg
White	441	1654
Black	71	209
Asian	21	30
Other/ unknown	11	51
Total	**544**	**1944**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria from the pivotal Phase III studies (MIT-Do001-C301 and MIT- Do001-C302) are discussed below:

Malignancies

- **History of malignancy, with the exception of basal cell or squamous cell carcinoma of the skin if diagnosed more than 1 year prior to the Screening visit.**
- **Any clinically significant findings found by the Investigator at the breast examination and/or on mammography suspicious of breast malignancy that would require additional clinical testing to rule out breast cancer (however, simple cysts confirmed by ultrasound are allowed).**
- **PAP test with atypical squamous cells undetermined significance (ASC-US) or higher (low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion [HSIL] [ASC-H], HSIL, dysplastic or malignant cells) in sub-totally hysterectomized and NH subjects. Note: ASC-US is allowed if a reflex human papilloma virus (HPV) testing is performed and is negative for high risk oncogene HPV subtypes 16 and 18.**
- **For NH subjects:**
  - **History or presence of uterine cancer, endometrial hyperplasia, or disordered proliferative endometrium;**
  - **Presence of endometrial polyps;**
  - **Undiagnosed vaginal bleeding or undiagnosed abnormal uterine bleeding;**
  - **Endometrial ablation;**
  - **Any uterine/endometrial abnormality that in the judgment of the investigator contraindicates the use of oestrogen and/or progestin therapy. This includes presence or history of adenomyosis or significant myoma.**

Reason for exclusion: the risk of occurrence of oestrogen-dependent malignancies such as endometrial cancer, breast cancer and ovarian cancer is influenced by HRT. The estimated risk of endometrial cancer in non-users of HRT is reported as 5 in every 1000 women. In women aged 45 to 74 years with a uterus who had taken oestrogen-alone HRT, there was a four-fold increase in risk of endometrial cancer (Beresford et al., 1997). The risk of breast cancer is increased in oestrogen-alone therapy after more than 5 years of use, whereas that risk is lower than 2-fold in women taking combined oestrogen-progestagen for the same duration. Use of both oestrogen-alone and oestrogen-progestagen therapies is associated with statistically significant but small increased risk of ovarian cancer in observational studies, with an estimate of one additional ovarian cancer death in 1,700 to 3,300 hormone therapy users. The exclusion criteria above were included to prevent patients with these conditions being at risk of malignancy progression or developing a malignancy.

Is it considered to be included as missing information? No

Rationale: the SmPC contraindicates HRT use in women with oestrogen-dependent malignancies or conditions predisposing to oestrogen-dependent malignancies. Oestrogen-dependent malignancies such as endometrial cancer, breast cancer and ovarian cancer are safety concerns for E4.

Cardiovascular

- **Systolic blood pressure (BP) higher than 130 mmHg, diastolic BP higher than 80 mmHg during screening.**
- **History of venous or arterial thromboembolic disease (e.g., superficial or deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, angina pectoris, etc.), or first-degree family history of VTE.**
- **History of known acquired or congenital coagulopathy or abnormal coagulation factors, including known thrombophilia's.**
- **Laboratory values of fasting glucose above 125 mg/dL (>6.94 mmol/L) and/or glycated haemoglobin above 7%.**
- **Dyslipoproteinemia (LDL >190 mg/dL [>4.91 mmol/L] and/or triglycerides >300 mg/dL [>3.39 mmol/L]).**
- **Subjects smoking >15 cigarettes per day.**
- **Systemic lupus erythematosus.**

Reason for exclusion: women younger than 60 years or who begin HRT less than 10 years after the onset of menopause are at a higher risk of VTE compared to placebo (RR, 1.74; 95% CI, 1.11-2.73) according to a 2015 Cochrane meta-analysis (Boardman et al., 2015). ATEs such as ischaemic stroke have an increased risk of 1.5-fold associated with the use of oestrogen-alone therapy and combination oestrogen-progestagen therapy. Women with risk factors for VTEs and ATEs were excluded from clinical studies to avoid confounders for the safety assessment of E4.

Is it considered to be included as missing information? No

Rationale: the SmPC contraindicates the use of HRT in women with a history or presence of VTE and ATE. VTE and ATE are important safety concerns for E4.

Gallbladder

Presence or history of gallbladder disease, unless cholecystectomy has been performed.

Reason for exclusion: the occurrence and deterioration of gallbladder disease and cholelithiasis has been reported with the use of hormone therapy, including hormonal replacement therapy. Women with a history of gallbladder disease who did not have a cholecystectomy or presence of gallbladder disease were excluded from clinical studies to avoid confounders for the safety assessment of estetrol monohydrate.

Is it considered to be included as missing information? No

Rationale: the SmPC warns that women with cholelithiasis aggravated during pregnancy or previous hormone treatment should be closely supervised.

Hepatic impairment

History of acute liver disease in the preceding 12 months before the start of screening or presence or history of chronic or severe liver disease [alanine transaminase (ALT) or aspartate transaminase (AST) >2x upper limit of normal (ULN), bilirubin >1.5 ULN], or liver tumours.

Reason for exclusion: oestrogen levels contribute to the risk of developing liver disease. Women with a presence or history of chronic or severe liver disease were excluded from the pivotal clinical studies to avoid confounders for the safety assessment of E4.

Is it considered to be included as missing information? No

Rationale: the SmPC contraindicates the use of E4 in women with severe liver disease as long as liver function tests have not returned to normal. Acute liver disease is not considered as important and has not been included in the list of safety concerns for E4.

Renal impairment

Chronic or current acute renal impairment (estimated glomerular filtration rate <60 ml/min).

Reason for exclusion: oestrogens may have an impact on renal health and may be reno-protective. Women with a history of acute renal impairment confirmed by a glomerular filtration rate < 60mL/min were excluded from the pivot clinical studies to avoid confounders for the safety assessment of E4.

Is it considered to be included as missing information? No

Rationale: the SmPC warns the use of E4 in women with moderate or severe renal impairment is not recommended and oestrogens may cause fluid retention and patients with renal dysfunction should be carefully observed. Chronic or acute renal impairment is not considered as important and has not been included in the list of safety concerns for E4.

Porphyria

Reason for exclusion: porphyria can be drug-induced by medications such as oestrogen-containing therapies.

Is it considered to be included as missing information? No

Rationale: the exclusion criterion above was included to prevent patients with porphyria being at risk of an acute attack during the study treatment. Porphyria is not considered as important and has not been included in the list of safety concerns for E4.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

Table 7: Limitations of clinical trial programme

Ability to detect adverse reactions	Limitation of clinical trial programme	Discussion of implications for target population
Which are rare	A total of 2759 female subjects were exposed to E4 in completed clinical trials in any population. Of note, a total of 2681 post-menopausal subjects were exposed to E4 in clinical trials.	Adverse drug reactions with combination therapy with a frequency greater than 1 in 960 could be detected if there were no background incidences.
Due to prolonged exposure	A total of 602 female subjects completed at least 365 days of treatment with E4 15 and 20 mg.	During a period of 12 months, there were no AEs which would correlate with prolonged exposure
Due to cumulative exposure		E4 does not accumulate in tissues and hence there is no potential for harm due to cumulative exposure
Due to long latency	Not specifically studied	There are no indications at this point for possible implications of long latency adverse drug reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 8: SIV.2: Exposure of special populations included or not in clinical trial development programme

Type of special population	Exposure
Pregnant women	0
Breastfeeding women	
Elderly (≥ 65 years)	79
Patients with: hepatic impairment renal impairment	- Hepatic impairment: 8 mild, 8 moderate and 8 severe - Renal impairment: 8 mild, 8 moderate and 8 severe
Patients with: cardiovascular impairment immunocompromised patients	0

Type of special population	Exposure
Population with relevant different ethnic origin	For E4 15 and 20 mg and for any other E4 doses: White 85.2% Black 10.2% Asian 2.1% Other/ unknown 2.5%
Subpopulations carrying relevant genetic polymorphisms	0

Part II: Module SV - Post-authorisation experience

Not applicable.

SV.1 Post-authorisation exposure

Not applicable

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no apparent potential for misuse of E4 for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table 9: SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risk	**Reason for not including an identified or potential risk in the list of safety concerns in the RMP**
	Class effects for HRTs and routine risk minimisation measures in the Product Information are sufficient to manage the following risks.
VTE	The relative risk of VTE has been reported as 1.3- to 3-fold increase with HRT.
ATE	There is an increased risk of 1.5-fold associated with the use of oestrogen-only and combined oestrogen-progestagen therapy.
Breast cancer	The risk of breast cancer is increased in oestrogen-only therapy users after more than 5 years of use. That risk is lower than the 2-fold increased risk in women taking combined oestrogen-progestagen therapy after more than 5 years of use.
Ovarian cancer	Women who used HRT for 5 years from age 50 years, had one extra ovarian cancer per 1000 users over non-users; the risk was increased even with < 5 years of use.

Venous thromboembolism (VTE)

The occurrence of an event of venous thromboembolism such as deep vein thrombosis or pulmonary embolism is more likely during the first year of use.

The risk is categorised as an important safety concern not relevant for risk management because it is well known to healthcare professionals, it rarely occurs and routine risk minimisation measures are deemed adequate to manage this risk.

Arterial thromboembolism (ATE)

The relative risk does not change with the duration of use of HRT or the woman's age, however, as the baseline risk of stroke is strongly age-dependent, a woman using HRT has an overall risk of stroke that increases with age.

The risk is categorised as an important safety concern not relevant for risk management because it is well known to healthcare professionals, it rarely occurs and routine risk minimisation measures are deemed adequate to manage this risk.

Breast cancer

In contrast to ischaemic stroke, the risk of breast cancer is dependent on the duration of use.

The risk is categorised as not relevant for risk management because it is well known to healthcare professionals and routine risk minimisation measures are deemed adequate to manage this risk.

Ovarian cancer

The risk of ovarian cancer declined the longer HRT had ceased, even though the excess risk for certain tumour types remained after 10 year stopping long-term treatment (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015).

The risk is categorised as not relevant for risk management because it is well known to healthcare professionals, rare and routine risk minimisation measures are deemed adequate to manage this risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks: no risks have been identified as important.

Important Potential Risk: Endometrium neoplasm malignancy

Evidence for risk to be added in the safety specification: It is well known from scientific publications that oestrogen-only hormone replacement therapy increases the risk of endometrial cancer. A 1.80 (95% CI 1.19–2.70) relative risk of endometrial cancer in current oestrogen-only HRT users was established (Million Women Study, 2005). Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65 (CMDh, 2024). However, progestogens counteract the proliferative effects of oestrogens on the endometrium and can prevent this increased risk. The risk of endometrial cancer was not altered in those who reported last using cyclic combined HRT (relative risk 1.05 [95% CI 0.91–1.22]) and was lower in women using continuous combined HRT (relative risk 0.71 [95% CI 0.56–0·90]) compared with never users (Million Women Study, 2005). No case of endometrial cancer was reported during the clinical development of E4.

Risk-benefit impact: The SmPC of estetrol is in line with the clinical practice i.e. in women with a uterus, a progestogen should be added continuously, thus the impact on the benefit-risk balance of the product is expected to be very low.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Table 10: Important potential risk: Endometrium neoplasm malignancy

Potential mechanism	Oestrogens play a mitogenic role in the normal endometrium, driving tissue growth as part of pregnancy anticipation during the menstrual cycle. In general, oestrogens, including 17β-oestradiol (E2), drive endometrial growth, and progestogens, including progesterone (P4), block endometrial growth and promote differentiation (Rodriguez et al., 2019). Two specific intracellular receptors, oestrogen receptor (ER) α and ERβ that mediate the biological effects of oestrogen actions, regulate cell growth and distinguish a variety of normal tissues from hormone-responsive tumours through interactions with cellular factors (Zhou et al., 2019). Oestrogen-dependent endometrial tumours usually express high levels of ER α and are thought to

	be hormonally driven (Wang et al., 2023). Oestrogen can signal through ER in a genomic, i.e. binding to the genome and regulate transcription, and a nongenomic manner i.e. activating signalling pathways (Rodriguez et al., 2019). However, the mechanisms of these factors contributing to the malignant state remain unclear.
Evidence source(s) and strength of evidence	No case of endometrial cancer was reported during the clinical development of E4. Endometrial cancer is a class effect of HRTs published in several scientific publications. There is an established increased risk of endometrial cancer with oestrogen-only HRT products, while there is little or no risk in case of sequential combined HRTs and continuous combined HRTs, respectively (Million Women Study, 2005).
Characterisation of the risk	The use of oestrogen-only HRT increases the risk of endometrial cancer. In the Million Women Study from 2005 the researchers established a 1.80 (95% CI 1.19–2.70) relative risk of endometrial cancer in current oestrogen-only HRT users. Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65 (CMDh, 2024). However, progestogens counteract the proliferative effects of oestrogens on the endometrium. The risk of endometrial cancer was not altered in those who reported last using cyclic combined HRT (relative risk 1.05 [95% CI 0.91–1.22]) and was lower in women using continuous combined HRT (relative risk 0.71 [95% CI 0.56–0·90]) compared with never users (Million Women Study, 2005). Abnormal uterine bleeding is the most frequent symptom of endometrial cancer, but many other disorders give rise to the same symptom. Endometrial cancer is primarily diagnosed histologically from endometrial tissue obtained with endometrial biopsy devices. Endometrial cancer is a surgically stage disease (FIGO stage) which is also the most important prognostic feature of the disease apart from myometrial invasion, histological type, and differentiation grade; most are independent of each other. The FIGO stage reflects the 5-year survival, which varies according to series but is around 85% for stage I, 75% for stage II, 45% for stage III, and 25% for stage IV disease (Amant et al., 2005).
Risk factors and risk groups	The following risks factors for endometrial cancers (Cramer, 2012) were identified: • Menstrual and reproductive events: early age at menarche, short or irregular cycle lengths, late age at menopause, late age at first birth, nulliparity, lack of breastfeeding, greater number of ovulatory cycles, oestrogen-only HRT use. • Medical history: obesity (high BMI), polycystic ovarian syndrome. • Habits and environmental factors: perineal use of talcum powder, lack of physical activity and exercise.

Preventability	Adding progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent the increased risk. In the Million Women Study, the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2) (CMDh, 2024). The SmPC of estetrol clearly states that in women with a uterus a progestogen approved for addition to oestrogen treatment should be added continuously.
Impact on the risk-benefit balance of the product	Impact on the risk-benefit balance of the product is expected to be very low since in clinical trials endometrium neoplasm malignancy was not observed and in clinical practice progestin dose is adjusted to signs and symptoms such as endometrial thickness and uterine bleeding to oppose oestrogen effect on endometrium.
Public health impact	A potential impact on public health is not anticipated.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table 11: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Endometrium neoplasm malignancy
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Specific adverse reaction follow-up questionnaires

In order to further characterise the important potential risk of 'Endometrium neoplasm malignancy' and to ensure high quality reports and facilitate better causality assessment, a targeted follow-up questionnaire is utilised for safety concern of 'Endometrium neoplasm malignancy'.

Considering that most of the initial post-marketing cases are poorly documented, targeted follow-up questionnaires provide help in better assessment of the cases and thus are considered necessary outstanding routine pharmacovigilance activities by Gedeon Richter Plc.

Targeted follow-up form can be found in Annex 4.

Other forms of routine pharmacovigilance activities

None proposed.

III.2 Additional pharmacovigilance activities

Feasibility report on potential real-world data study

Study title:

Feasibility report on potential real-world data study to further characterise the important potential risk of endometrium neoplasm malignancy with estetrol used in HRT

Rationale and study objectives:

The purpose of the feasibility analysis is to investigate whether real-world data study is suitable to characterise a rare potential risk of endometrium neoplasm malignancy in patients exposed to FYLREVY, considering the required sample size, data sources and the expected market uptake of estetrol in non-hysterectomised women for such study.

Study design:

Real world evidence, retrospective

Study population:

Postmenopausal non-hysterectomised women exposed to FYLREVY

Milestones:

Feasibility report to be submitted within 3 months after European Commission Decision (June 2026)

III.3 Summary table of additional pharmacovigilance activities

Table 12: Part III.1: On-going and planned additional pharmacovigilance activities

Study and status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Feasibility report on potential real-world data study Planned	To investigate whether real-world data study is suitable to characterise a rare potential risk of 'endometrium neoplasm malignancy' in patients exposed to FYLREVY, considering the required sample size, data sources and the expected market uptake of estetrol in non-hysterectomised women for such study	Important potential risk of 'endometrium neoplasm malignancy'	Feasibility report	Within 3 months after European Commission Decision (June 2026)

Part IV: Plans for post-authorisation efficacy studies

Table 13: Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 14: Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Endometrium neoplasm malignancy	Routine risk communication: • Description of endometrial cancer risk is included in SmPC sections 4.3, 4.4, 4.8 and 5.1. • Description of endometrial cancer risk is included in PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Posology instruction that progestogen should be added continuously in women with a uterus in SmPC section 4.2 and PL section 3. • Contraindication in patients with known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer) in SmPC section 4.3 and PL section 2 • Warning that oestrogens alone for prolonged periods increases the risk of endometrial hyperplasia and carcinoma in women with intact uterus and the excess risk can be prevented with the addition of progestogen in continuous combined oestrogen-progestogen therapy in SmPC section 4.4 and PL section 2. • Precaution about break-through bleeding and spotting after some time on therapy and instruction that it should be investigated to rule out endometrial malignancy in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Table 15: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endometrium neoplasm malignancy	Routine risk minimisation measures: • SmPC section 4.2, 4.3, 4.4, 4.8 and 5.1 • PL section 2, 3 and 4 • Prescription-only medicine Additional risk minimisation measures: No additional risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire Additional pharmacovigilance activities: • Feasibility report on potential real-world data study

Part VI: Summary of the risk management plan

Summary of risk management plan for FYLREVY (estetrol 14.2 mg and 18.9 mg)

This is a summary of the risk management plan (RMP) for FYLREVY. The RMP details important risks of FYLREVY, how these risks can be minimised, and how more information will be obtained about FYLREVY's risks and uncertainties (missing information).

FYLREVY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FYLREVY should be used.

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

Important new concerns or changes to the current ones will be included in updates of FYLREVY's RMP.

I. The medicine and what it is used for

FYLREVY is authorised for oral hormone replacement therapy in hysterectomised post-menopausal women and non-hysterectomised post-menopausal women with at least 12 months since last menses. It contains estetrol monohydrate as the active substance.

Further information about the evaluation of FYLREVY's benefits can be found in FYLREVY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of FYLREVY, together with measures to minimise such risks and the proposed studies for learning more about FYLREVY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of FYLREVY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FYLREVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 16: List of important risks

List of important risks and missing information	
Important identified risks	None
Important potential risks	Endometrium neoplasm malignancy (cancerous tumour that forms in the inner lining of the womb)
Missing information	None

II.B Summary of important risks

Table 17: Summary of important risks

Important potential risk: Endometrium neoplasm malignancy (cancerous tumour that forms in the inner lining of the womb)	
Evidence for linking the risk to the medicine	No case of endometrial cancer was reported during the clinical development of E4. Endometrial cancer is a class effect of HRTs published in several scientific publications. There is an established increased risk of endometrial cancer with oestrogen-only HRT products, while there is little or no risk in case of sequential combined HRTs and continuous combined HRTs, respectively (Million Women Study, 2005).
Risk factors and risk groups	The following risks factors for endometrial cancers (Cramer, 2012) were identified: • Menstrual and reproductive events: early age at menarche, short or irregular cycle lengths, late age at menopause, late age at first birth, no children, lack of breastfeeding, greater number of ovulatory cycles, oestrogen-only HRT use • Medical history: obesity (high body mass index), polycystic ovarian syndrome • Habits and environmental factors: perineal use of talcum powder, lack of physical activity and exercise
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC section 4.2, 4.3, 4.4, 4.8 and 5.1

	• PL section 2, 3 and 4 • Prescription-only medicine Additional risk minimisation measures: No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Feasibility report on potential real-world data study See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of FYLREVY.

II.C.2 Other studies in post-authorisation development plan

Feasibility report on potential real-world data study

Purpose of the study:

The purpose of the feasibility analysis is to investigate whether real-world data study is suitable to characterise a rare potential risk of endometrium neoplasm malignancy in patients exposed to FYLREVY, considering the required sample size, data sources and the expected market uptake of estetrol in non-hysterectomised women for such study.

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted follow-up form for 'Endometrium neoplasm malignancy'

FYLREVY TARGETED FOLLOW-UP FORM

for Endometrium neoplasm malignancy

PATIENT INFORMATION			
Patient initials	……..	Ethnic origin	☐ Caucasian/white
Age at the time of event	……..		☐ Asian
Date of birth	../../…. *(dd/mm/yyyy)*		☐ Black
Height	…….. cm		
Weight	…….. kg		☐ Other, specify ……..
BMI	…….. kg/m^2		
Patient's alcohol consumption details		Alcohol: ☐ Yes ☐ No If yes, unit per day: ……..	

FYLREVY TREATMENT DETAILS				
FYLREVY				
Indication:	……..		Batch number	……..
Dates (treatment duration if dates known)		Route	Total daily dose	Dosing frequency
Start: ../../…. *(dd/mm/yyyy)*	Stop: ../../…. *(dd/mm/yyyy)*	……..	……..	……..
Added progestogen			☐ Yes, provide details below ☐ No, provide details ……	
Indication:	……..		Type	……..
Dates (treatment duration if dates known)		Route	Total daily dose	Dosing regimen
Start: ../../…. *(dd/mm/yyyy)*	Stop: ../../…. *(dd/mm/yyyy)*	……..	……..	☐ Continuous ☐ Sequential: …... (days)

MEDICAL HISTORY/ PAST MEDICATIONS	
Any history of polycystic ovary syndrome (PCOS)?	☐ Yes ☐ No If yes, provide details …… ……
Any history of diabetes?	☐ Yes ☐ No If yes, provide details …… ……
Any history of insulin resistance?	☐ Yes ☐ No If yes, provide details …… ……

Did the patient experience any other cancer(s) in the past?	☐ Yes ☐ No If yes, provide cancer type: …….. Did the patient receive any therapy(ies) for this cancer? ☐ Yes ☐ No If yes, provide details …… ……
Did the patient use any intrauterine device (IUD) in the past?	☐ Yes ☐ No If yes, provide details …… ……
Does the patient have any medical history of endometrial hyperplasia?	☐ Yes ☐ No If yes, provide details …… ……
Does the patient have any family history of endometrial, ovarian, breast and/ or colorectal cancers?	☐ Yes ☐ No If yes, provide details …… ……
Was the patient previously treated with any hormonal therapy (including contraceptives or other HRTs)?	☐ Yes ☐ No If yes, provide details …… ……
Information on any other relevant medical history/ past medications?	☐ Yes ☐ No If yes, provide details …… ……
Information on patient's physical activity?	☐ Yes ☐ No If yes, frequency: ☐ Daily ☐ 1-2 times a week ☐ 3-4 times a week

CONCOMITANT MEDICATION INFORMATION Did the patient take any medications in the 2 months preceding the reported event?				
Medication	Route/ Dose	Indication	Start date	Stop date
……..	……..	……..	../../…. *(dd/mm/yyyy)*	../../…. *(dd/mm/yyyy)*
……..	……..	……..	../../…. *(dd/mm/yyyy)*	../../…. *(dd/mm/yyyy)*
……..	……..	……..	../../…. *(dd/mm/yyyy)*	../../…. *(dd/mm/yyyy)*

OBSTETRIC HISTORY	
Age at menarche	……..
Menstrual cycles in adulthood	☐ Irregular ☐ Regular

	Lengths: …….. days
Number of previous pregnancies:	……..
Live births: ……..	Still births: ……..
Miscarriages: ……..	Ectopic pregnancies: ……..
Elective terminations: ……..	Molar pregnancies: ……..
Age at first birth	……..
Breastfeeding	☐ Yes ☐ No ☐ Not applicable
Age at menopause	……..

ADVERSE EVENT INFORMATION	
Description of the endometrium neoplasm malignancy	…… ……
Event diagnosis (biopsy) date	../../…. *(dd/mm/yyyy)*
Event stop date confirmed by another biopsy or hysterectomy	../../…. *(dd/mm/yyyy)*
Outcome of the event	☐ Not recovered/ unchanged ☐ Recovered ☐ Improving/ recovering ☐ Recovering with sequalae ☐ Fatal ☐ Unknown
Action taken with FYLREVY in response to this event	☐ Treatment continued ☐ Treatment withdrawn ☐ Dose reduced ☐ Dose increased ☐ Treatment interrupted ☐ Unknown ☐ Not applicable
Action taken with added progestogen if applicable	☐ Treatment continued ☐ Treatment withdrawn ☐ Dose reduced ☐ Dose increased ☐ Treatment interrupted ☐ Unknown ☐ Not applicable
Did FYLREVY cause the adverse event?	☐ Certain ☐ Probable/ likely ☐ Possible ☐ Unlikely ☐ Unassessable
Did the co-administered progestogen contribute to the adverse event, e.g. insufficient dose?	☐ Yes ☐ No If yes, provide details …… ……

Could you provide Stage (FIGO) of endometrial cancer?	☐ Stage IA (tumour limited to endometrium) ☐ Stage IB (invasion of less than half the myometrium) ☐ Stage IC (invasion of more than half the myometrium) ☐ Stage IIA (endocervical glandular involvement only) ☐ Stage IIB (cervical stromal invasion) ☐Stage IIIA (tumour invading serosa or adnexa, or malignant peritoneal cytology) ☐ Stage IIIB (vaginal metastasis) ☐ Stage IIIC (metastasis to pelvic or para-aortic lymph nodes) ☐ Stage IVA (tumour invasion of the bladder or bowel mucosa) ☐ Stage IVB (distant metastases including intra-abdominal or inguinal nodes)
Could you provide the Grading of endometrial cancer at the time of diagnosis?	☐ Grade 1 (the cells are slower growing and look more like normal tissue) ☐ Grade 2 (the cells are growing at a speed of and look like cells somewhere between grades 1 and 3) ☐ Grade 3 (the cancer cells look very different form normal cells and will probably grow and spread faster)
Did the patient experience vaginal bleeding and/ or spotting before this diagnosis?	☐ Yes ☐ No If yes, provide Frequency of bleeding/ spotting: …….. Duration of bleeding/ spotting: …….. Volume of the bleeding (number of sanitary protections per day): ……..
Was transvaginal ultrasound performed on this patient before this diagnosis?	☐ Yes ☐ No If yes, endometrial thickness measured: Transvaginal ultrasound (date: ../../…. *(dd/mm/yyyy)*): …….. mm Transvaginal ultrasound (date: ../../…. *(dd/mm/yyyy)*): …….. mm Transvaginal ultrasound (date: ../../…. *(dd/mm/yyyy)*): …….. mm
Was the endometrial cancer diagnosis confirmed by a biopsy?	☐ Yes ☐ No If yes, date of the biopsy ../../…. *(dd/mm/yyyy)* If no, provide information on how the endometrial cancer was diagnosed ……...
Was any endometrial biopsy performed on this patient prior to this diagnosis?	☐ Yes ☐ No If yes, result of the biopsy (date: ../../…. *(dd/mm/yyyy)*): ……..

Was any radiological intervention performed on this patient e.g. MRI or PET after diagnosis?	☐ Yes ☐ No If yes, provide details ……. …….
Is the patient currently undergoing any medical treatment for endometrial carcinoma?	☐ Yes ☐ No If yes, provide details ……. …….
Is the patient currently undergoing any radiological treatment for endometrial carcinoma?	☐ Yes ☐ No If yes, provide details ……. …….
Was any surgery performed?	☐ Yes ☐ No If yes, provide details (type of surgery, histology result) ……. …….
Please provide any further information that you may consider relevant	……. …….