ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg film-coated tablets

Yselty 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yselty 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of linzagolix (as choline salt).

Excipient(s) with known effect
Each film-coated tablet contains 119.4 mg lactose.

Yselty 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of linzagolix (as choline salt).

Excipient(s) with known effect
Each film-coated tablet contains 238.8 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yselty 100 mg film-coated tablets

Round, pale yellow, film-coated tablets of 10 mm diameter, debossed “100” on one side and plain-faced on the other side.

Yselty 200 mg film-coated tablets

Oblong, pale yellow, film-coated tablets of 19 mm by 9 mm, debossed “200” on one side and plain-faced on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yselty is indicated for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

4.2 Posology and method of administration

Posology

Yselty treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of uterine fibroids.

Pregnancy must be ruled out prior to initiating treatment with Yselty.

Yselty should preferably be started in the first week of the menstrual cycle and should be taken continuously once daily.

The recommended dose of Yselty is:

- 100 mg or, if needed, 200 mg once daily with concomitant hormonal add-back therapy (ABT, estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily), see section 5.1.
- 100 mg once daily for women in whom ABT is not recommended or who prefer to avoid hormonal therapy (see section 5.1)
- 200 mg once daily for short-term use (< 6 months) in clinical situations when reduction of uterine and fibroid volume is desired (see section 5.1). Fibroid size may increase when the treatment is stopped. Due to the risk of bone mineral density (BMD) decrease with prolonged use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months.

In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) scan is recommended prior to starting Yselty treatment (see section 4.4).

Yselty can be taken without interruption. A DXA scan is recommended after 1 year of treatment for all women, and there is a need for continued BMD monitoring thereafter (see section 4.4).

Missed dose
If a dose is missed, treatment must be taken as soon as possible and then continued the next day at the usual time.

Special populations
Hepatic impairment
No dose adjustment is necessary in women with mild or moderate hepatic impairment (Child-Pugh A or B). Yselty should be avoided in women with severe hepatic impairment (Child-Pugh C) (see sections 4.4 and 5.2).

Renal impairment
Prescribers are recommended to monitor for adverse reactions in women who have mild renal impairment (eGFR = 60-89 mL/min; see section 4.4 and 5.2) although no dose adjustment is required. Yselty should be avoided in women with moderate (eGFR = 30-59 mL/min), severe renal impairment (eGFR < 30 mL/min) or end-stage renal disease (see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of Yselty in children aged under 18 years for the indication of treatment of moderate to severe symptoms of uterine fibroids.

Method of administration

Oral use.

Yselty can be taken with or without food (see section 5.2).

The 200 mg dose can be taken as either one 200 mg tablet or two times a 100 mg tablet.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Pregnancy or breast-feeding (see section 4.6)
- Known osteoporosis
- Genital bleeding of unknown aetiology
- Contraindications related to ABT should be respected if concomitant ABT is given

4.4 Special warnings and precautions for use

Medical examination/consultation

Prior to the initiation or reinstitution of Yselty, a complete medical history (including family history) must be taken. Blood pressure must be measured, and a physical examination must be performed guided by the contraindications (see section 4.3) and warnings for use (see section 4.4). During treatment, periodic check-ups must be carried out according to standard clinical practice.

Any hormonal contraception needs to be stopped prior to initiation of Yselty. Pregnancy must be ruled out prior to administering or re-initiation of Yselty

Bone mineral density

In some women treated with Yselty, who had normal bone mineral density (BMD) at start of treatment, BMD loss varying from > 3-8% was reported.

The benefits and risks of Yselty in patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss (such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, and low body weight), including those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants), should be considered prior to initiating treatment. It is recommended to perform a DXA scan before commencing treatment with Yselty in these at-risk patients.

Further, a DXA scan is recommended after 1 year of treatment for all women to verify that the patient does not have an unwanted degree of BMD loss. Thereafter, depending on the prescribed dose of Yselty, BMD assessment is recommended annually (Yselty 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (Yselty 100 mg with concomitant ABT and Yselty 200 mg with concomitant ABT).

If the risks of BMD decrease exceed the potential benefit of treatment with Yselty, treatment should be discontinued.

Hepatic impairment

Yselty should be avoided in women with severe hepatic impairment (Child-Pugh C). No dose adjustment is necessary in women with mild or moderate hepatic impairment (Child-Pugh A or B), see section 4.2 and 5.2.

Renal impairment

Yselty should be avoided in women with moderate (eGFR = 30–59 mL/min), severe renal impairment (eGFR < 30 mL/min) or end-stage renal disease (see section 4.2). Prescribers are recommended to monitor for adverse reactions in women who have mild renal impairment (eGFR = 60-89 mL/min; see section 5.2) although no dose adjustment is required (see section 4.2).

Cardiovascular disorders/QT prolongation

Linzagolix marginally increases the QT interval but showed no evidence of clinically relevant risk of QT prolongation or Torsade de Pointes (see section 5.1). Caution should be exercised in patients who have known cardiovascular disease, family history of QT prolongation or hypokalaemia, and in concomitant use with medicinal products known to prolong the QT interval. Caution should also be exercised in patients with co-existing disorders leading to increased linzagolix plasma levels (see section 5.2).

Contraception

Linzagolix with or without concomitant ABT has not been demonstrated to provide contraception. Women of childbearing potential at risk of pregnancy have to use effective non-hormonal contraception while on treatment with Yselty (see section 4.6).

Change in menstrual bleeding pattern and reduced ability to recognise pregnancy

Women should be informed that treatment with Yselty usually leads to a significant reduction in menstrual blood loss and often leads to amenorrhoea, which may reduce the ability to recognise the occurrence of a pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected, and treatment should be discontinued if pregnancy is confirmed (see section 4.3 and 4.6).

Liver enzymes

Asymptomatic transient liver enzyme elevations have been reported (see section 4.8). Patients should be instructed to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Treatment should be discontinued if jaundice develops. Acute liver test abnormalities may necessitate discontinuation of treatment with linzagolix until liver tests return to normal.

Women with abnormal hepatic function parameters (≥2 upper limit of normal, ULN) were excluded from studies with linzagolix. Therefore, in women with known abnormal hepatic history, a baseline level of hepatic function tests should be obtained, and further regular monitoring should be performed. These patients should be treated with caution.

Lipid levels

Increases in lipid levels were observed with linzagolix treatment (see section 5.1). These increases were generally of no clinical relevance. However, in women with pre-existing elevated lipid profiles monitoring of lipid levels is recommended.

Mood disorders

Mood disorders including depression, alterations in mood, and emotional lability have been observed with treatment with GnRH antagonists including linzagolix (see section 4.8). Caution is to be applied in women with a history of depression and/or suicidal ideation. Patients with known depression or history of depression should be carefully monitored during treatment. Treatment should be discontinued if depression recurs to a serious degree.

CYP2C8 substrates

Use of Yselty should be avoided in patients using CYP2C8 sensitive substrate medicinal products with a narrow therapeutic index (e.g., paclitaxel, sorafenib and repaglinide, see section 4.5). It is recommended to monitor for increases in adverse reactions associated with other CYP2C8 substrates when co-administered with Yselty.

Warnings and precautions relevant to ABT

If concomitant ABT is prescribed, all warnings and precautions relevant to ABT should be considered.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

CYP2C8 substrate medicinal products

Linzagolix has been shown to increase mean repaglinide (a CYP2C8 sensitive substrate) exposure in healthy subjects by less than 2-fold. Due to the risk of increased plasma concentrations, concomitant administration of Yselty and medicinal products primarily cleared by CYP2C8 metabolism and with a narrow therapeutic index such as paclitaxel, sorafenib and repaglinide, should be avoided (see section 4.4). Prescribers are recommended to monitor for increases in adverse reactions associated with other CYP2C8 substrates when co-administered with Yselty.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Linzagolix with or without ABT has not been demonstrated to provide contraception. Women of childbearing potential at risk of pregnancy have to use effective non-hormonal contraception while on treatment with Yselty.

Pregnancy

There are no or limited amount of data from the use of linzagolix in pregnant women.
Studies in animals have shown that exposure to linzagolix early in pregnancy may increase the risk of early pregnancy loss (see section 5.3). Based on the pharmacological effects, an adverse effect on pregnancy cannot be excluded.

Yselty is contraindicated during pregnancy (see section 4.3). Treatment should be discontinued if pregnancy is confirmed.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of linzagolix in milk (for details see 5.3).

It is unknown whether linzagolix/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Yselty is contraindicated during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

Yselty has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported in the pivotal phase 3 clinical studies were hot flushes and headaches, which were reported with higher frequency at higher doses and less frequently when ABT was taken concomitantly (referred to as "with ABT"). Hot flushes were reported in 5.2%, 9.6%, 10.1% and 31% of women treated with 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively. Similarly, headaches were reported more frequently at higher doses and decreased with ABT (1.4%, 2.4%, 4% and 6.2% for 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively). All other adverse reactions listed below were reported in fewer than 3% of subjects.

Tabulated list of adverse reactions

Adverse reactions associated with linzagolix are reported based on pooled data from two pivotal phase 3 studies which included 828 patients with uterine fibroids who received linzagolix and 209 patients who received placebo up to 6 months. These are tabulated in Table 1 below.

Adverse reactions listed in Table 1 are classified by frequency category and MedDRA system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions from pivotal clinical studies

	Linzagolix 100 mg	**Linzagolix 100 mg with ABT**	**Linzagolix 200 mg**	**Linzagolix 200 mg with ABT**
Psychiatric disorders				
Common	Mood disorders[a]/*	Mood disorders[a]/* Libido decreased	Mood disorders[a]/* Libido decreased	Mood disorders[a]/* Libido decreased
Uncommon	Libido decreased			
Nervous system disorders				
Common	Headache	Headache	Headache	Headache
Vascular disorders				
Very Common	Hot flush		Hot flush	
Common		Hot flush		Hot flush Hypertension
Uncommon	Hypertension	Hypertension	Hypertension	
Gastrointestinal disorders				
Common		Nausea/vomiting Upper abdominal pain	Nausea/vomiting Constipation	Nausea/vomiting
Uncommon	Upper abdominal pain		Upper abdominal pain	Constipation
Hepatobiliary disorder				
Common	Elevated liver enzymes*	Elevated liver enzymes*	Elevated liver enzymes*	Elevated liver enzymes*
Skin and subcutaneous tissue disorders				
Common	Hyperhidrosis		Hyperhidrosis Night sweats	
Uncommon	Night sweats			Night sweats
Musculoskeletal and connective tissue disorders				
Common	Arthralgia	Bone mineral density decreased*	Arthralgia Bone mineral density decreased*	Arthralgia
Uncommon	Bone mineral density decreased*			Bone mineral density decreased*
Reproductive system and breast disorders				
Common	Vaginal haemorrhage[b]/* Pelvic pain Change in menstrual bleeding pattern [c]/*	Vaginal haemorrhage[b]/* Pelvic pain	Vaginal haemorrhage[b]/* Pelvic pain Vulvovaginal dryness	Vaginal haemorrhage[b]/* Pelvic pain Change in menstrual bleeding pattern [c]/*
Uncommon	Vulvovaginal dryness	Vulvovaginal dryness Change in menstrual bleeding pattern[c]/*	Change in menstrual bleeding pattern[c]/*	
General disorders and administration site conditions				
Common	Asthenia			
Uncommon			Asthenia	Asthenia

ABT: estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily

*see sections 4.4 and/or 4.8, Description of selected adverse reactions, for further information

[a]Mood disorders includes reports of mood swings, affect lability, emotional disorder, irritability, mood altered, anxiety, depression, depressed mood

[b]Vaginal haemorrhage includes reports of vaginal haemorrhage, metrorrhagia, menorrhagia, menometrorrhagia and uterine haemorrhage

[c]Change in menstrual bleeding pattern includes reports of menstruation delayed, irregular menstruation and amenorrhea

Description of selected adverse reactions

Mood disorders
The most common mood disorder adverse reactions were reports of mood swings, which were reported in up to 1.5% of subjects in all linzagolix dose groups. Affect lability and anxiety were reported in 0.6% of subjects on linzagolix. Anxiety was only reported in the 200 mg groups with or without ABT. Reports of depression and depressed mood were infrequent. No more than 1 subject in each of the linzagolix treatment groups reported depression or depressed mood in the phase 2 or phase 3 clinical studies. For specific recommendations, refer to section 4.4.

Elevated liver enzymes
Asymptomatic increases in hepatic enzyme levels, mainly alanine and aspartate transaminase (ALT and AST), were reported. Most increases were low grade and generally returned to normal during continued treatment. The incidence of ALT and/or AST increases in the linzagolix groups was below 3%. In approximately 1% of subjects, ALT/AST levels increased to at least 3 times ULN, with the highest increases reported with linzagolix 200 mg or 200 mg with ABT. No concurrent bilirubin elevation was observed. For specific recommendations, refer to section 4.4.

Bone mineral density changes
The effect of linzagolix on BMD was assessed by DXA scan. In the two phase 3 clinical studies, dose- and time-dependent changes in BMD were observed. Concomitant ABT attenuated BMD loss (see Table 2).
Changes in BMD were most pronounced with the 200 mg dose; following 6 months of treatment, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were observed in 55% and 4% of patients, respectively.
Following 12 months of treatment with linzagolix 100 mg, 100 mg with ABT and 200 mg with ABT, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were observed in 38% and 7%, 16% and 0% and 27% and 1% of patients, respectively.

Table 2: Proportion of patients with lumbar spine BMD change from baseline >3% and >8% at 24 weeks and at 52 weeks of treatment in PRIMROSE 1 and 2

	Linzagolix 100 mg	**Linzagolix 100 mg with ABT**	**Linzagolix 200 mg**	**Linzagolix 200mg with ABT**
24 weeks of treatment				
Percentage of subjects (%) with BMD CfB > 3% / >8%	36 / 3	20 / 0	55 / 4	26 / 1
52 weeks of treatment				
Percentage of subjects (%) with BMD CfB > 3% / >8%	38 / 7	16 / 0	-*	27 / 1

ABT: estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily, CfB: change from baseline
* Linzagolix 200 mg was studied up to 6 months

At 6 months after the end of treatment, increases of BMD were noted in all treatment groups, indicating partial recovery. For specific recommendations, refer to sections 4.2 and 4.4. For detailed information on BMD decrease refer to section 5.1.

Vaginal haemorrhage
Vaginal haemorrhage (including reports of vaginal haemorrhage, uterine haemorrhage, metrorrhagia, menorrhagia, and menometrorrhagia) was reported during treatment with linzagolix. The most frequent adverse reactions were vaginal haemorrhage, metrorrhagia and menorrhagia which were reported in 13 (1.6%), 11 (1.3%) and 5 (0.6%) of subjects treated with linzagolix, respectively. Vaginal haemorrhage was reported more frequently in subjects in the 100 mg and 200 mg linzagolix

with ABT group (up to 2.4%) compared to the groups without ABT (1%). Metrorrhagia was reported in 3 (1.5%), 3 (1.4%), 1 (0.5%) and 4 (1.9%) of subjects in the 100 mg, 100 mg with ABT, 200 mg, and 200 mg with ABT groups, respectively, and menorrhagia was reported for 1 (0.5%), 1 (0.5%), 2 (1.0%) and 1 (0.5%) of subjects in the linzagolix 100 mg, 100 mg with ABT, 200 mg and 200 mg with ABT groups, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

In cases of overdose, patients should be monitored closely, and management should be symptomatic and supportive.

For women taking regimens with concomitant ABT, overdose of estrogen and progestin may cause hormone-related symptoms, including but not limited to nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-gonadotropin-releasing hormones, ATC code: H01CC04.

Mechanism of action

Linzagolix is a selective, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist that inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland, thereby modulating the hypothalamic-pituitary-gonadal axis.

Pharmacodynamic effects

Effects on pituitary and ovarian hormones
Administration of linzagolix results in dose-dependent suppression of luteinizing hormone and follicle-stimulating hormone, leading to decreased blood concentrations of estradiol and progesterone. In the phase 3 studies, full suppression of serum estradiol (median < 20 pg/mL) was observed with linzagolix 200 mg from 4 to 24 weeks. Partial suppression was observed with linzagolix 100 mg, 100 mg with concomitant ABT (referred to as “with ABT”) and 200 mg with ABT from 4 to 52 weeks, with median serum estradiol levels in the range of 20 to 60 pg/mL. Progesterone levels were maintained ≤ 3.1 ng/mL in 83% of women receiving linzagolix 200 mg for 24 weeks and 68% of women receiving linzagolix 100 mg for 52 weeks, and about 90% of women receiving linzagolix 100 mg with ABT or 200 mg with ABT for 52 weeks.

Cardiac electrophysiology
One randomised, placebo- and positive-controlled, open-label, single-dose, crossover thorough-QTc study evaluated the effect of linzagolix on the QTc interval. Forty-eight healthy women received a 200 mg dose of linzagolix (therapeutic target exposure), a 700 mg dose of linzagolix (supratherapeutic target exposure), a 400 mg dose of moxifloxacin (positive control), or placebo with an appropriate washout. A marginal effect with linzagolix 200 mg and 700 mg doses on the prolongation of the heart-rate corrected QT interval was identified, with a maximum observed mean at 3 hours post dose of 8.34 msec (90% CI 6.44 - 10.23) and 9.92 msec (90% CI 8.03 - 11.81), respectively. Based on the magnitude of the QTc prolongation, subsequent concentration effect modelling and QT subinterval (JTpeakc), the observed effects are not considered clinically relevant. The highest anticipated steady state concentration in the QT study was estimated in healthy subjects, not accounting for increases in unbound linzagolix exposure due to existing disorders (see section 5.2).

Changes in lipid parameters
Fasting lipid levels (HDL, LDL and total cholesterol, and triglycerides) were assessed every three months from start of linzagolix treatment up to 3 months post treatment. There were increases in LDL cholesterol, HDL cholesterol, and triglycerides across all linzagolix arms (typically less than 15% in the case of LDL, and less than 20% in the case of triglycerides) and generally increases were higher for the linzagolix only regimes. These increases were evident from week 12 and lipid parameters had generally stabilised after 52 weeks of treatment. After stopping linzagolix, lipid levels showed signs of returning towards baseline by 12 weeks after stopping treatment, but still remained slightly elevated relative to baseline (see section 4.4).

Clinical efficacy and safety

The efficacy of Yselty was evaluated in two phase 3, randomised, double-blind and placebo-controlled studies, PRIMROSE 1 and PRIMROSE 2, including 511 and 501 women, respectively. PRIMROSE 1 was conducted in the US and PRIMROSE 2 was conducted primarily in Europe with about 10% of subjects being from the US. The studies had essentially replicate design with 52 weeks of treatment and 24 weeks post treatment follow-up. There are no on-treatment efficacy or safety data beyond 52 weeks.

Eligible patients had heavy menstrual bleeding (HMB: > 80 mL menstrual blood loss [MBL]/cycle) and a myomatous uterus with at least one fibroid ≥ 2 cm confirmed by ultrasound and no myoma > 12 cm. MBL was measured using the alkaline haematin method.

The mean age of women was 42 years (range 20 to 58), and mean body mass index was 29.9 kg/m^2 (range 16.8 to 58.6). Approximately 34.5% of women were Black, 63.5% were White and 2% were of other races. The most commonly reported symptoms, in addition to HMB, were abdominal pain (67.9% of women), abdominal pressure (52.5%), menstruation lasting longer than usual (50.4%), lower back pain (50.2%), increased urinary frequency (34.5%) and pain during intercourse (27.7%). The median uterine volume was 241 cm^3 (range 32 to 2075 cm^3) and the median fibroid volume was 53 cm^3 (range 0 to 1142 cm^3). Almost all women (99.7%) had at least one fibroid ≥ 2 cm long and 97.5% had FIGO classification from 1 to 6.

Subjects were randomised to one of 5 treatments: placebo, Yselty 100 mg, Yselty 200 mg, Yselty 100 mg with concomitant ABT (estradiol 1 mg/ norethisterone acetate 0.5 mg, referred to as “with ABT”) or Yselty 200 mg with ABT, all taken once daily. Subjects randomised to placebo or Yselty 200 mg were switched to Yselty 200 mg with ABT after 24 weeks except in PRIMROSE 1, in which 50% of placebo subjects continued placebo until 52 weeks.

The primary efficacy endpoint was a response, defined as having an MBL of ≤ 80 mL and ≥ 50% reduction from baseline over the last 28 days before week 24. Treatment with Yselty with or without ABT resulted in a higher proportion of women with reduced MBL at week 24 compared to placebo. The percentage of responders was 56.4%, 66.4%, 71.4% and 75.5% with Yselty 100 mg, 100 mg with ABT, 200 mg and 200 mg with ABT, respectively in PRIMROSE 1 and 56.7%, 77.2%, 77.7% and 93.9% respectively in PRIMROSE 2 (Table 3). At week 52, the percentage of responders was 57.4%,

79.9% and 87.9% with Yselty 100 mg, 100 mg with ABT and 200 mg with ABT, respectively, in PRIMROSE 1 and 53.2%, 91.3% and 91.6%, respectively, in PRIMROSE 2.

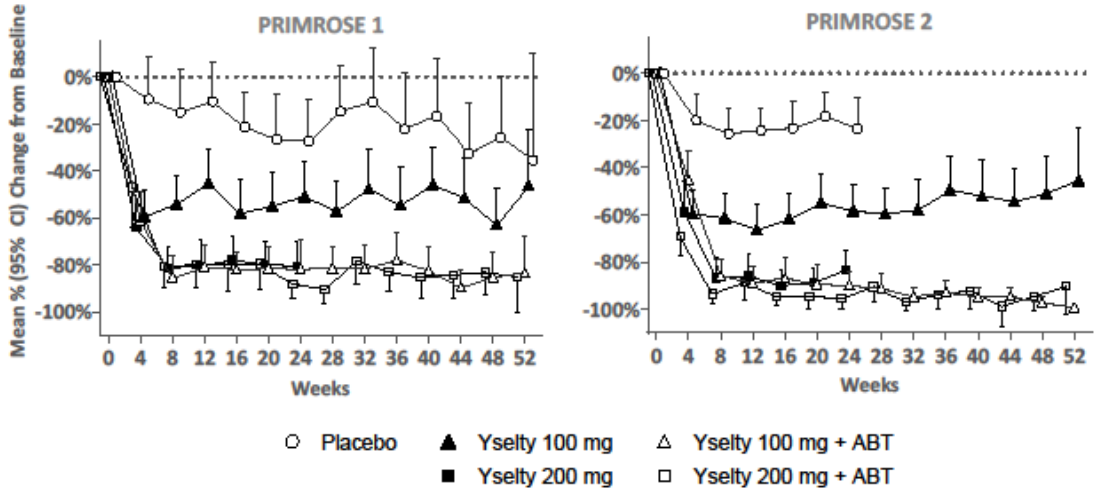
Table 3: Responders (women with reduced menstrual blood loss) at 24 weeks

Study	PRIMROSE 1					PRIMROSE 2				
Treatment	Placebo	Yselty				Placebo	Yselty			
		100 mg	100 mg + ABT	200 mg	200 mg + ABT		100 mg	100 mg + ABT	200 mg	200 mg + ABT
N	103	94	107	105	102	102	97	101	103	98
Percentage (95% CI) of responders[1, 2]	35.0 (25.8, 45.0)	56.4 (45.8, 66.6)	66.4 (56.6, 75.2)	71.4 (61.8, 79.8)	75.5 (66.0, 83.5)	29.4 (20.8, 39.3)	56.7 (46.3, 66.7)	77.2 (67.8, 85.0)	77.7 (68.4, 85.3)	93.9 (87.1, 97.7)

[1] Responders were women with ≤ 80 mL MBL and ≥ 50% reduction from baseline
[2] Clopper-Pearson 95% CI. p-values ≤0.003 for odds-ratio to placebo from a Cochran-Mantel-Haenszel test with race as stratification factor.
ABT: estradiol 1 mg/norethisterone acetate 0.5 mg

The mean percentage reduction in MBL over time is shown in Figure 1. Treatment with Yselty 100 mg achieved a maximal effect of about 60% reduction in MBL by 4 weeks. Treatment with Yselty 100 mg with ABT or 200 mg with or without ABT, reached a maximal effect of about 80 to 95% reduction in MBL by 8 weeks. These reductions were maintained up to 52 weeks.

Figure 1: Mean percentage change in menstrual blood loss for each 28-day period up to week 52



In both pivotal phase 3 studies, improvements were observed in secondary endpoints after 24 weeks in the Yselty dose groups compared to placebo (Table 4), including an increased proportion of women achieving amenorrhea, reduced pain scores, higher haemoglobin levels in anaemic patients (< 12 g/dL at baseline) and increased health-related quality of life scores. These improvements were more pronounced with Yselty 200 mg (with or without ABT) and Yselty 100 mg with ABT as compared to Yselty 100 mg.

Improvements in secondary endpoints at 24 weeks were generally maintained after 52 weeks in the Yselty 100 mg with and without ABT and Yselty 200 mg with ABT groups. Uterine and fibroid volumes were markedly and consistently reduced after 24 weeks, only in the Yselty 200 mg without ABT group. In PRIMROSE 1 and 2, respectively, uterine volumes were reduced by 31% and 43%, and fibroid volumes were reduced by 43% and 49%. Mean uterine and fibroid volumes increased toward baseline volumes when ABT was added after 6 months of treatment with Yselty 200 mg without ABT.

Table 4: Secondary endpoints at 24 weeks

Study	PRIMROSE 1					PRIMROSE 2				
Treatment	Placebo	Yselty				Placebo	Yselty			
		100 mg	100 mg + ABT	200 mg	200 mg + ABT		100 mg	100 mg + ABT	200 mg	200 mg + ABT
N	103	94	107	105	102	102	97	101	103	98
Percentage of women with amenorrhea (95% CI)[1]	21.4 (13.9, 30.5)	38.3 (28.5, 48.9)	42.1 (32.6, 52.0)	60.0 (50.0, 69.4)	57.8 (47.7, 67.6)	11.8 (6.2, 19.6)	34.0 (24.7, 44.3)	63.4 (53.2, 72.7)	70.9 (61.1, 79.4)	80.6 (71.4, 87.9)
Mean change from baseline in haemoglobin levels – g/dL (SD, n)[2]	0.30 (1.57, 45)	1.36 (1.82, 42)	1.87 (1.57, 52)	2.22 (1.58, 53)	2.00 (1.60, 50)	0.38 (1.69, 43)	1.36 (1.50, 49)	1.88 (1.58, 45)	2.10 (1.77, 46)	2.27 (1.43, 47)
Estimated mean change from baseline in pain score (95% CI)[3]	-1.06 (-1.74, -0.37)	-2.70 (-3.38, -2.02)	-3.11 (-3.81, -2.41)	-3.85 (-4.47, -3.23)	-3.68 (-4.34, -3.01)	-0.44 (-1.14, 0.27)	-1.61 (-2.35, -0.88)	-1.91 (-2.64, -1.18)	-2.55 (-3.25, -1.84)	-2.27 (-3.00, -1.55)
Estimated mean ratio to baseline in uterine volume (95% CI)	1.02 (0.91, 1.15)	0.83 (0.74, 0.94)	1.06 (0.94, 1.20)	0.69 (0.62, 0.77)	0.92 (0.82, 1.03)	1.04 (0.92, 1.17)	0.85 (0.75, 0.96)	0.88 (0.77, 0.99)	0.57 (0.50, 0.64)	0.80 (0.71, 0.91)
Estimated mean ratio to baseline in fibroid volume (95% CI)	0.95 (0.75, 1.19)	0.75 (0.60, 0.94)	0.98 (0.77, 1.24)	0.57 (0.46, 0.70)	0.88 (0.70, 1.09)	1.04 (0.84, 1.29)	0.85 (0.68, 1.06)	0.93 (0.75, 1.17)	0.51 (0.41, 0.63)	0.79 (0.63, 0.99)
Estimated mean change from baseline in HRQL score (95% CI)[4]	15.5 (9.4, 21.6)	26.1 (20.0, 32.2)	37.2 31.0, 43.5)	35.5 (29.8, 41.1)	34.2 (28.3, 40.1)	10.3 (4.0, 16.6)	20.6 (14.1, 27.2)	22.9 (16.4, 29.5)	30.2 (23.9, 36.5)	30.7 (24.2, 37.1)

[1] Amenorrhea was defined as no menstrual blood detected by the alkaline hematin method (not including spotting or MBL < 1 to 3 mL) for 35 days and until the end of the treatment up to 24 weeks

[2] In women with baseline anaemia (haemoglobin < 12 g/dL). n represents the number of women with non-missing data at 24 weeks

[3] Pain was assessed using a 0 to 10 numerical rating scale (NRS).

[4] The Health-Related Quality of Life (HRQL) score is a part of the validated Uterine Fibroid Symptoms – Quality of Life (UFS-QoL) questionnaire. The score is from 0 to 100 with a higher score indicating better health-related quality of life. The baseline score was about 40.

ABT estradiol 1 mg/norethisterone acetate 0.5 mg; SD standard Deviation; CI confidence interval

Bone mineral density

BMD was assessed using DXA scan at baseline, during treatment (Weeks 24 and 52) and 6 months after the end of treatment (week 76). Subjects at significant risk of osteoporosis, with a history of or known osteoporosis or other metabolic bone disease were excluded from PRIMROSE 1 and PRIMROSE 2 trials.

Mean percentage BMD decreases observed at 24 and 52 weeks were dose- and time-dependent and attenuated by concomitant ABT (Table 5).

At 24 weeks, the change in BMD was most pronounced in women who had full estradiol suppression with Yselty 200 mg (-3.70%). This regimen was not continued for more than 6 months (see section 4.2). The changes were less pronounced in women who received other regimens: -1.99% with Yselty 100 mg, -0.96% Yselty 100 mg with ABT and -1.13% with Yselty 200 mg with ABT.

At 52 weeks, the mean percentage changes from baseline indicated a reduced rate of BMD loss: -2.36% with Yselty 100 mg, -0.93% with Yselty 100 mg with ABT and -1.61% with Yselty 200 mg with ABT. The level of treatment induced BMD loss in this population considered to be clinically meaningful is

not well established, and will depend on the individual woman, but in general BMD losses of approximately 3% or more should be reviewed and monitored carefully. It is important to consider the individual woman's baseline BMD, age and overall osteoporosis risk profile when assessing an individual woman's BMD loss, and the benefit-risk of continuing treatment.

At 24 weeks after stopping treatment, most patients had full or partial recovery of lumbar spine BMD: 53%, 52% and 64% for Yselty 100 mg, 100 mg with ABT and 200 mg with ABT, respectively in PRIMROSE 1 and 59%, 80% and 67% for Yselty 100 mg, 100 mg with ABT and 200 mg with ABT in PRIMROSE 2.

The extent and rate of BMD loss when treating women beyond 12 months is currently unknown.

Table 5: Mean percent change from baseline (CfB) in lumbar spine BMD after 24 and 52 weeks of treatment in PRIMROSE 1 and 2

	Placebo	**Yselty 100 mg**	**Yselty 100 mg+ABT**	**Yselty 200 mg***	**Yselty 200 mg+ABT**
24 weeks of treatment					
Number of subjects	130	121	122	138	127
Mean percent CfB	0.46	-1.99	-0.96	-3.70	-1.13
95% CI	0.06; 0.85	-2.47; -1.50	-1.45; -0.48	-4.18; -3.22	-1.60; -0.66
52 weeks of treatment					
Number of subjects	19	93	84	-	97
Mean percent CfB	-0.83 **	-2.36	-0.93	-	-1.61
95% CI	-2.08; 0.42	-3.10; -1.63	-1.40; -0.47	-	-2.22; -0.99

* Yselty 200 mg was studied up to 6 months.
** Placebo was used up to 12 months in PRIMROSE 1.

Effects on endometrium
Endometrial biopsies were performed in a subset of patients at baseline, week 24 and week 52 as part of the safety assessment in both phase 3 studies. Results did not raise any safety concerns.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Yselty in all subsets of the paediatric population in treatment of leiomyoma of uterus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single dose of 100 mg or 200 mg, linzagolix is swiftly absorbed, with C_{max} occurring approximately 2 h after administration. Linzagolix shows dose-linear pharmacokinetics and no relevant accumulation at steady state.

Administration of linzagolix (200 mg) with a high fat meal appeared to delay and to slightly decrease peak plasma concentrations, consistent with delayed gastric emptying after the high fat meal but had no effect on the extent of exposure. It is not considered to be of clinical significance.

Distribution

Linzagolix was highly bound (> 99%) to plasma proteins, in particular to albumin, and did not partition into red blood cells. The volume of distribution (Vd/F) following 7 consecutive days of oral linzagolix 100 mg or 200 mg administration was 11.067 L (CV: 20.4%) and 11.178 L (CV: 11.8%), respectively.

Biotransformation

Metabolite profiling and identification of linzagolix quantified up to 7 metabolites across plasma, urine, and faeces. The predominant component in the human plasma profiles was unchanged linzagolix. Similarly, linzagolix was the predominant component in urine and one of the major components in faeces. All plasma metabolites were present at less than 10% of the total linzagolix related exposure.

Elimination

Following multiple doses of linzagolix, linzagolix $t_{1/2}$ was approximately 15 hours. Linzagolix was mainly excreted in urine and approximately one third was eliminated via faeces. Following administration of multiple doses of linzagolix 100 mg and 200 mg, the linzagolix geometric mean apparent clearance (CL/F) was 0.522 L/h (CV: 20.1%) and 0.499 L/h (CV: 15.2%), respectively.

Special populations

The population PK analysis suggests that age does not have a meaningful effect on linzagolix exposure. The analysis showed that Black subjects had a 22.5% decrease in CL/F relative to Caucasian subjects; however, the safety profile of linzagolix between Black and Caucasian subjects was similar.

Based on the population PK analysis, weight was found to influence linzagolix PK. The CL/F in patients weighing 52.7 kg (5th percentile) was predicted to be about 19.2% lower, and in patients weighing 112 kg (95th percentile), about 42% higher than in patients weighing 70 kg. However, subgroup analyses of data from the pivotal phase 3 studies did not indicate any clinically relevant differences with respect to safety and efficacy, and no dose adjustment is recommended.

Hepatic impairment
A clinical study conducted in female subjects with hepatic impairment (mild Child-Pugh A, moderate: Child-Pugh B and severe: Child-Pugh C) revealed no relevant effect on total plasma linzagolix exposure following administration of a single 200 mg dose of linzagolix. The unbound fraction of linzagolix was not affected by mild and moderate hepatic impairment; no dose adjustments with Yselty in patients with mild and moderate hepatic impairment are required (see section 4.2). Yselty should not be used in women with severe hepatic impairment (Child-Pugh C) as 2- to 3-fold higher unbound linzagolix mean exposures were recorded (see section 4.4).

Renal impairment
A clinical study conducted in female subjects with renal impairment (mild, moderate, severe and end-stage renal disease) where glomerular filtration rate (GFR) was assessed using creatine clearance, revealed no relevant effect on total plasma linzagolix exposure following administration of a single 200 mg dose of linzagolix. Unbound plasma linzagolix C_{maxu}, AUC_{u0-t}, and AUC_{u0-inf} were increased by 30%, 32%, and 33%, in women with mild renal impairment as compared to healthy subjects with normal renal function. As a potential safety concern with long-term use cannot be excluded, prescribers are recommended to monitor for adverse reactions in women with mild renal impairment (see section 4.4). However, no dose adjustment is required (see section 4.2). Yselty should not be used in women with moderate or severe renal impairment or end-stage renal disease as approximately 1.5-fold (in moderate) and 2-fold (in severe renal impairment and ESRD) higher unbound linzagolix mean exposures were observed (see section 4.4).

5.3 Preclinical safety data

Reproductive and developmental toxicity
Due to its mechanism of action, linzagolix prevented conception and reduced implantation in rat fertility studies and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies.

No teratogenic effects and no adverse effect on the pre- and postnatal development were observed in a rat study.
Dose levels of 100 mg/kg and 3 mg/kg linzagolix were shown to be the No observed adverse effect level (NOAEL) for reproductive function and embryo-foetal development in the main embryo-development studies in rat and rabbit, respectively (corresponding to respectively 5.9 and 0.004 times the maximum recommended human dose based on AUC).

Lactation
Linzagolix was shown to be excreted in milk of rats. Up to 96 h after administration, the radioactivity concentration was lower in milk than in plasma (less than 0.3 times).

Mutagenicity
A standard battery of in vitro and in vivo tests revealed no evidence of mutagenic or clinically relevant genotoxic potential of the drug.

Carcinogenicity
Carcinogenic properties of linzagolix were assessed in a 26-week carcinogenicity study in transgenic Tg RasH2 mice. There was no evidence of linzagolix-induced carcinogenicity up to the highest dose of 500 mg/kg (corresponding to 13.2 times the maximum recommended dose in humans based on AUC).

In a 2-year carcinogenicity study in rats, an increased incidence of uterine endometrial adenocarcinoma was observed in the mid- (50 mg/kg) and high-dose (500 mg/kg) groups (corresponding to respectively 6.8 and 9.6 times the maximum recommended human dose based on AUC) and a marginal increase in the frequency of mammary gland adenocarcinoma was observed at the mid-dose (50 mg/kg) only (6.8 times the maximum recommended human dose based on AUC). The clinical relevance of these findings remains unknown.

Non-carcinogenic histopathological findings in the ovary and uterus (mouse) or ovary and female mammary gland (rat) were considered to be related to the pharmacological action of linzagolix.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose, microcrystalline
Low-substituted hydroxypropylcellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate

Film-coating

Macrogol poly(vinyl alcohol) grafted copolymer (E1209)
Talc (E553b)
Titanium dioxide (E171)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVDC/aluminium blister containing 14 film-coated tablets per blister.

Pack size of 28 film-coated tablets (two blisters of 14 film-coated tablets) per cardboard box.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64

Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/001
EU/1/21/1606/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Patheon France
40 boulevard de Champaret
38300 Bourgoin Jallieu
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard box for 100 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg film-coated tablets
linzagolix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of linzagolix (as choline salt).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yselty 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 100 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg tablets
linzagolix

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Theramex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard box for 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 200 mg film-coated tablets
linzagolix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of linzagolix (as choline salt).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yselty 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 200 mg tablets
linzagolix

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Theramex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Yselty 100 mg film-coated tablets
linzagolix

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yselty is and what it is used for

Yselty contains the active substance linzagolix. It is used to treat moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are noncancerous tumours of the uterus (womb). Yselty is used in adult women (over 18 years of age) of childbearing age. In some women, uterine fibroids may cause heavy menstrual bleeding (your 'period') and pelvic pain (pain below the belly button).

Linzagolix blocks the action of a hormone, gonadotropin releasing hormone, that helps to regulate the release of female sex hormones estradiol and progesterone. These hormones trigger women's periods (menstruation). When blocked, the levels of the hormones estrogen and progesterone circulating in the body are reduced. By decreasing their levels, linzagolix stops or reduces menstrual bleeding and decreases pain and pelvic discomfort and other symptoms associated with uterine fibroids.

2. What you need to know before you take Yselty

Do not take Yselty
If you have any of the conditions listed below:

- if you are allergic to linzagolix or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant or if you think you might be pregnant or if you are breast-feeding
- if you have osteoporosis (a condition that makes bones fragile)
- if you have any genital bleeding of unknown origin.

If you are taking Yselty together with additional hormonal therapy of estradiol and norethisterone acetate (also known as add-back therapy), follow the instructions in the "Do not take…" section of the package leaflets for estradiol and norethisterone acetate.

Warnings and precautions
Talk to your doctor or pharmacist before taking Yselty.

Before you start treatment with Yselty, your doctor will discuss your medical and family history and relevant risk factors with you. Your doctor will also need to check your blood pressure and make sure you are not pregnant. You may also need a physical examination and additional checks before you start treatment, such as a scan to measure how strong your bones are, that will be specific to your medical needs and/or concerns.

Stop taking Yselty and get urgent medical attention if you notice:
- signs of liver disease:
  - yellowing of your skin or the whites of your eyes (jaundice).
  - nausea or vomiting, fever, severe tiredness.
  - dark urine, itching or upper abdominal pain.
- if you become pregnant.

Talk to your doctor or pharmacist before taking Yselty if you have:
- reduced liver or kidney function.
  Yselty is not recommended in women with severely reduced liver or moderately or severely reduced kidney function as the linzagolix blood level may become too high.
- increased levels of liver enzymes in the blood.
  Temporary increased levels of liver enzymes in the blood without symptoms may occur during treatment with Yselty.
- heart or blood circulation problems, a family history of changes in the electrical activity of the heart known as "QT prolongation" or you are taking a medicine that changes the electrical activity in the heart.
- increased blood fat levels (cholesterol). These levels should be monitored during treatment as Yselty may lead to further increases.
- had a fracture that was not caused by a major trauma, or other risks of bone mineral loss or reduced bone density. Yselty can lower bone mineral density, so your doctor may want to check it beforehand in this case.
- previously suffered from depression, mood changes, thoughts about suicide or any depressive symptoms as these have been reported with medications that work in the same way as Yselty does.
- if you think you might be pregnant. Yselty usually leads to a significant reduction or may even stop your menstrual bleeding (your 'period') during treatment and for a few weeks afterwards, making it difficult to recognise pregnancy. See under "Pregnancy and breast-feeding.

Yselty has not been shown to provide contraception. See under "Pregnancy and breast-feeding".

Yselty can be used together with another tablet containing the hormones estradiol and norethisterone acetate (also known as hormonal add-back therapy). If prescribed to you, read the leaflet of the tablet containing these hormones carefully as well as this leaflet.

Children and adolescents
Yselty is not recommended for children and adolescents under 18 years as it has not been studied in this age group.

Other medicines and Yselty
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including hormonal contraception.

Particularly inform your doctor or pharmacist if you are taking:

- repaglinide (a medicine used to treat diabetes)
- paclitaxel, sorafenib (medicines used to treat cancer)

Yselty is not recommended if you are using one of these medicines.

Pregnancy and breast-feeding
Do not use Yselty if you are pregnant or breast-feeding as it might harm your baby. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you become pregnant, stop taking Yselty and contact your doctor. Because Yselty reduces or stops your periods it might be difficult to recognise pregnancy. Carry out a pregnancy test if there is any chance you may be pregnant.

Women who could become pregnant should use effective non-hormonal contraception when taking Yselty.

Driving and using machines
Yselty has no influence on the ability to drive and use machines.

Yselty contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Yselty

Treatment with Yselty will be prescribed by a doctor who is experienced in the care of patients with uterine fibroids. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will work out the right dose of Yselty for you. **The following dose options are possible**:

- Either 100 mg Yselty (one tablet) or 200 mg Yselty (two tablets of 100 mg), taken once daily together with another tablet once daily containing the hormones estradiol and norethisterone acetate (also known as add-back therapy). If your doctor prescribes this add-back therapy, it is important to always take it with your Yselty tablets as this will help to reduce side effects including the risk and extent of bone mineral density loss.

- For women for whom estradiol and norethisterone acetate are not suitable, Yselty can be taken in a dose of one tablet of 100 mg daily alone, i.e. without estradiol and norethisterone acetate.

- For short-term use (up to 6 months only), Yselty 200 mg daily (two tablets of 100 mg) can be given without estradiol and norethisterone acetate to treat symptoms associated with large fibroid or uterine size.

Take the recommended dose **once daily**.
Start taking Yselty preferably in the first week of your menstrual cycle, which is the week you have bleeding.
Swallow the tablet(s) with one glass of water, with or without food.

Duration of use
Your doctor will work out how long to continue treatment, based on the risk of bone mineral density loss. The 200 mg dose (two tablets of 100 mg) without add-back therapy should be prescribed for no longer than 6 months.
Your doctor will check your bone mineral density by arranging a scan after the first 12 months of Yselty treatment to see if treatment can continue. If you continue Yselty treatment beyond one year, your doctor will keep checking your bone mineral density at regular intervals.

If you take more Yselty than you should
Tell your doctor if you think you have taken too much Yselty.

There have been no reports of serious harmful effects from taking several doses of this medicine at once. If Yselty is used together with the additional hormonal therapy of estradiol and norethisterone acetate, overdose of the hormones may cause nausea and vomiting, breast tenderness, stomach pain, drowsiness, fatigue and withdrawal bleeding.

If you forget to take Yselty
If you miss a dose, take it as soon as you remember and then resume taking your tablet the next day as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Yselty
If you would like to stop taking Yselty, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects can occur with the following frequencies:
Very common (may affect more than 1 in 10 people)
- hot flush

Common (may affect up to 1 in 10 people)
- mood disorders, such as mood swings, affect lability (i.e. rapid changes in emotions), anxiety, depression, irritability, emotional disorder
- excessive, irregular, or prolonged bleeding from the womb (uterine bleeding)
- vaginal dryness
- pelvic pain
- joint pain
- headache
- reduction in bone mineral density or bone strength
- increased liver enzyme blood levels
- nausea (feeling sick), vomiting, pain in stomach region
- constipation
- decreased interest in sex (libido)
- weakness
- increased sweating
- night sweats
- high blood pressure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Yselty

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and cardboard box after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Yselty contains
- The active substance is linzagolix.
  One tablet of Yselty 100 mg contains 100 mg linzagolix.
- The other ingredients are:
  Tablet core: lactose monohydrate, microcrystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylcellulose, croscarmellose sodium and magnesium stearate. See section 2 “Yselty contains lactose and sodium”.
  Film-coating: macrogol poly(vinyl alcohol) grafted copolymer (E1209), talc (E553b), titanium dioxide (E171) and iron oxide yellow (E172).

What Yselty looks like and contents of the pack
Yselty 100 mg film-coated tablets are round shaped of 10 mm diameter, pale yellow, engraved with “100” on one side and plain on the other side.

Yselty is provided in a cardboard box with 2 blisters containing 14 film-coated tablets (tablet) per blister.

Pack size: 28 film-coated tablets

Marketing Authorisation Holder
Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

Manufacturer
Patheon France
40 boulevard de Champaret
38300 Bourgoin Jallieu
France

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the patient

Yselty 200 mg film-coated tablets
linzagolix

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yselty is and what it is used for

Yselty contains the active substance linzagolix. It is used to treat moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are noncancerous tumours of the uterus (womb). Yselty is used in adult women (over 18 years of age) of childbearing age. In some women, uterine fibroids may cause heavy menstrual bleeding (your 'period') and pelvic pain (pain below the belly button).

Linzagolix blocks the action of a hormone, gonadotropin releasing hormone, that helps to regulate the release of female sex hormones estradiol and progesterone. These hormones trigger women's periods (menstruation). When blocked, the levels of the hormones estrogen and progesterone circulating in the body are reduced. By decreasing their levels, linzagolix stops or reduces menstrual bleeding and decreases pain and pelvic discomfort and other symptoms associated with uterine fibroids.

2. What you need to know before you take Yselty

Do not take Yselty
If you have any of the conditions listed below:

- if you are allergic to linzagolix or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant or if you think you might be pregnant or if you are breast-feeding
- if you have osteoporosis (a condition that makes bones fragile)
- if you have any genital bleeding of unknown origin.

If you are taking Yselty together with additional hormonal therapy of estradiol and norethisterone acetate (also known as add back therapy), follow the instructions in the "Do not take…" section of the package leaflets for estradiol and norethisterone acetate.

Warnings and precautions
Talk to your doctor or pharmacist before taking Yselty.

Before you start treatment with Yselty, your doctor will discuss your medical and family history and relevant risk factors with you. Your doctor will also need to check your blood pressure and make sure you are not pregnant. You may also need a physical examination and additional checks before you start treatment, such as a scan to measure how strong your bones are, that will be specific to your medical needs and/or concerns.

Stop taking Yselty and get urgent medical attention if you notice:
- signs of liver disease:
  - yellowing of your skin or the whites of your eyes (jaundice).
  - nausea or vomiting, fever, severe tiredness.
  - dark urine, itching or upper abdominal pain.
- if you become pregnant.

Talk to your doctor or pharmacist before taking Yselty if you have:
- reduced liver or kidney function.
  Yselty is not recommended in women with severely reduced liver or moderately or severely reduced kidney function as the linzagolix blood level may become too high.
- increased levels of liver enzymes in the blood.
  Temporary increased levels of liver enzymes in the blood without symptoms may occur during treatment with Yselty.
- heart or blood circulation problems, a family history of changes in the electrical activity of the heart known as "QT prolongation" or you are taking a medicine that changes the electrical activity in the heart.
- increased blood fat levels (cholesterol). These levels should be monitored during treatment as Yselty may lead to further increases.
- had a fracture that was not caused by a major trauma, or other risks of bone mineral loss or reduced bone density. Yselty can lower bone mineral density, so your doctor may want to check it beforehand in this case.
- previously suffered from depression, mood changes, thoughts about suicide or any depressive symptoms as these have been reported with medications that work in the same way as Yselty does.
- if you think you might be pregnant. Yselty usually leads to a significant reduction or may even stop your menstrual bleeding (your 'period') during treatment and for a few weeks afterwards, making it difficult to recognise pregnancy. See under "Pregnancy and breast-feeding.

Yselty has not been shown to provide contraception. See under "Pregnancy and breast-feeding".

Yselty can be used together with another tablet containing the hormones estradiol and norethisterone acetate (also known as hormonal add-back therapy). If prescribed to you, read the leaflet of the tablet containing these hormones carefully as well as this leaflet.

Children and adolescents
Yselty is not recommended for children and adolescents under 18 years as it has not been studied in this age group.

Other medicines and Yselty
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including hormonal contraception.

Particularly inform your doctor or pharmacist if you are taking:

- repaglinide (a medicine used to treat diabetes)
- paclitaxel, sorafenib (medicines used to treat cancer)

Yselty is not recommended if you are using one of these medicines.

Pregnancy and breast-feeding
Do not use Yselty if you are pregnant or breast-feeding as it might harm your baby. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you become pregnant, stop taking Yselty and contact your doctor. Because Yselty reduces or stops your periods it might be difficult to recognise pregnancy. Carry out a pregnancy test if there is any chance you may be pregnant.

Women who could become pregnant should use effective non-hormonal contraception when taking Yselty.

Driving and using machines
Yselty has no influence on the ability to drive and use machines.

Yselty contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Yselty

Treatment with Yselty will be prescribed by a doctor who is experienced in the care of patients with uterine fibroids. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will work out the right dose of Yselty for you. **The following dose options are possible for Yselty 200 mg tablets**:

- One tablet of 200 mg Yselty taken once daily together with another tablet once daily containing the hormones estradiol and norethisterone acetate (also known as add-back therapy). If your doctor prescribes this add-back therapy, it is important to always take it with your Yselty tablets as this will help to reduce side effects including the risk and extent of bone mineral density loss.

- For short-term use (up to 6 months only), one tablet of Yselty 200 mg once daily can be given without estradiol and norethisterone acetate to treat symptoms associated with large fibroid or uterine size.

It should be noted that a dose of 100 mg Yselty can be used if a lower dose is required.

Take the recommended dose **once daily**.
Start taking Yselty preferably in the first week of your menstrual cycle, which is the week you have bleeding.
Swallow the tablet with one glass of water, with or without food.

Duration of use
Your doctor will work out how long to continue treatment, based on the risk of bone mineral density loss. The 200 mg dose without add-back therapy should be prescribed for no longer than 6 months.

Your doctor will check your bone mineral density by arranging a scan after the first 12 months of Yselty treatment to see if treatment with estradiol and norethisterone acetate can continue. If you continue Yselty treatment beyond one year, your doctor will keep checking your bone mineral density at regular intervals.

If you take more Yselty than you should
Tell your doctor if you think you have taken too much Yselty.

There have been no reports of serious harmful effects from taking several doses of this medicine at once. If Yselty is used together with the additional hormonal therapy of estradiol and norethisterone acetate, overdose of the hormones may cause nausea and vomiting, breast tenderness, stomach pain, drowsiness, fatigue and withdrawal bleeding.

If you forget to take Yselty
If you miss a dose, take it as soon as you remember and then resume taking your tablet the next day as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Yselty
If you would like to stop taking Yselty, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects can occur with the following frequencies:
Very common (may affect more than 1 in 10 people)
- hot flush

Common (may affect up to 1 in 10 people)
- mood disorders, such as mood swings, affect lability (i.e. rapid changes in emotions), anxiety, depression, irritability, emotional disorder
- excessive, irregular, or prolonged bleeding from the womb (uterine bleeding)
- vaginal dryness
- pelvic pain
- joint pain
- headache
- reduction in bone mineral density or bone strength
- increased liver enzyme blood levels
- nausea (feeling sick), vomiting, pain in stomach region
- constipation
- decreased interest in sex (libido)
- weakness
- increased sweating
- night sweats
- high blood pressure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Yselty

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and cardboard box after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Yselty contains

- The active substance is linzagolix.
  One tablet of Yselty 200 mg contains 200 mg linzagolix.
- The other ingredients are:
  Tablet core: lactose monohydrate, microcrystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylcellulose, croscarmellose sodium and magnesium stearate. See section 2 “Yselty contains lactose and sodium”.
  Film-coating: macrogol poly(vinyl alcohol) grafted copolymer (E1209), talc (E553b), titanium dioxide (E171) and iron oxide yellow (E172).

What Yselty looks like and contents of the pack
Yselty 200 mg film-coated tablets are oblong (19 × 9 mm), pale yellow, engraved with “200” on one side and plain on the other side.

Yselty is provided in a cardboard box with 2 blisters containing 14 film-coated tablets (tablet) per blister.

Pack size: 28 film-coated tablets

Marketing Authorisation Holder
Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

Manufacturer
Patheon France
40 boulevard de Champaret
38300 Bourgoin Jallieu
France

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu