swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Yselty

International non-proprietary name:	linzagolix (as linzagolix choline)
Pharmaceutical form:	Film-coated tablets
Dosage strength(s):	100 mg and 200 mg
Route(s) of administration:	Oral
Marketing authorisation holder:	Future Health Pharma GmbH
Marketing authorisation no.:	69692
Decision and decision date:	approved on 19.01.2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for linzagolix, as linzagolix choline, in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Treatment of hypermenorrhoea associated with fibroids in adult women before the onset of menopause.

A bone density measurement must be carried out with dual X-ray absorptiometry (DXA scan) before starting treatment with Yselty in patients with risk factors for osteoporosis or bone density loss (see "Warnings and precautions").

2.2.3 Requested dosage

Summary of the requested standard dosage:
- 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).
- 100 mg once daily for women in whom ABT is not recommended or who prefer to avoid hormonal therapy.
- 200 mg once daily for short-term use (< 6 months) in clinical situations when reduction of uterine and fibroid volume is desired. 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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	01 December 2023
Formal objection	19 December 2023
Response to formal objection	11 January 2024
Formal control completed	15 January 2024
List of Questions (LoQ)	23 May 2024
Response to LoQ	19 September 2024
Preliminary decision	14 March 2025
Response to preliminary decision	16 July 2025
Labelling corrections and/or other aspects	6 October 2025
Response to labelling corrections and/or other aspects	5 November 2025
2nd Labelling corrections and/or other aspects	28 November 2025
Response to 2nd labelling corrections and/or other aspects	18 December 2025
Final decision	19 January 2026
Decision	approval

3 Medical context

Uterine fibroids, or myomas, are benign, hormone-sensitive, soft tissue tumours of the uterus. In premenopausal women, they represent the most common type of tumour of the reproductive system. Their growth is promoted particularly by oestrogens and also progesterone.
The prevalence of fibroids is about 70% by the age of 50 years. During the fertile phase of life, the incidence increases with age. Fibroids usually regress spontaneously after menopause.
Most fibroids are asymptomatic, and only around a quarter of affected women develop symptoms that require treatment. The most common is heavy menstrual bleeding (HMB), meaning an increase in both intensity and duration of menstrual bleeding. Fibroid-induced HMB is one of the main reasons for hysterectomy. The second most common symptom is pain, mostly associated with HMB.

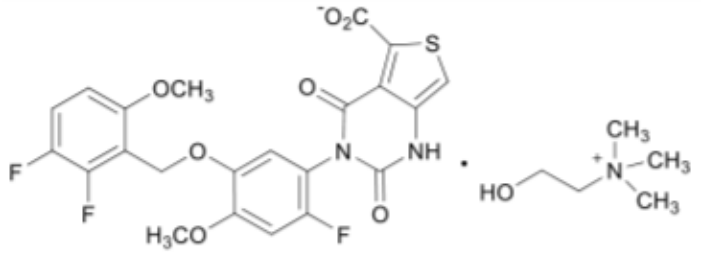
The current gold standard in the diagnosis of fibroids is transvaginal ultrasound, surgery (most commonly hysterectomy or fibroid enucleation) used to be the standard treatment.
In recent years, gynaecological endocrinologists are increasingly advocating medical treatment for fibroid-associated symptoms, not least because of the not inconsiderable morbidity and mortality associated with a hysterectomy or fibroid enucleation. However, until recently, drug-based therapeutic options have been limited.
The most effective treatment for fibroid-associated HMB are GnRH analogues which, at the same time, also reduce fibroid size. In Switzerland, only goserelin (Zoladex®) is authorised for the treatment of fibroids, and only "for preoperative pretreatment of anaemic patients with uterine fibroids, in conjunction with iron therapy".
GnRH analogues act by suppressing oestrogen to castration levels. They primarily reduce the heavy bleeding caused by fibroids and thereby – together with iron therapy – also have a positive effect on anaemia. They also reduce the volume of the fibroids as well as the total uterine volume; it is unknown, however, if the reduction of volume is of any clinical significance. Use of GnRH analogues is limited by their safety profile, i.e. particularly the induction of menopause symptoms (particularly vasomotor symptoms, VMS), but also depressive episodes. The most serious risk is a reduction in bone mineral density (BMD), which limits duration of use to 3-6 months in all non-malignant indications. In order to extend this treatment period, they are sometimes used together with a so-called “add-back therapy” (ABT), i.e. the concurrent administration of an oestrogen-progestogen combination or tibolone.
A further drawback of GnRH analogues is the occurrence of a flare effect at the start of treatment, caused by an initial rise in the secretion of FSH and LH, i.e. the intensity of bleeding can increase temporarily. Consequently, although GnRH analogues have proved to be effective in the treatment of fibroids, their use in everyday clinical practice is limited.

Oral, non-peptide GnRH antagonists like Yselty (linzagolix) represent an alternative option, which can also be used as longer-term therapy. These active substances may be used as monotherapy or combined with ABT. The aim of combination therapy is to achieve oestrogen levels ensuring adequate efficacy while at the same time mitigating the adverse effects, particularly BMD loss and VMS.

4 Quality aspects

4.1 Drug substance

INN: Linzagolix Choline
Chemical name: 2-Hydroxy-N,N,N-trimethylethanaminium 3-{5-[(2,3-difluoro-6-methoxyphenyl)methoxy]-2-fluoro-4-methoxyphenyl}-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-5-carboxylate
Molecular formula: $C_{22}H_{14}F_3N_2O_7S \bullet C_5H_{14}NO$
Molecular mass: 611.59 g/mol
Molecular structure:



Physicochemical properties: White to off-white powder, not hygroscopic, soluble in water.

Synthesis: Linzagolix is synthesised in a multi-step chemical synthesis using well-defined starting materials with acceptable specifications.

Specification: In order to ensure a consistent quality of linzagolix, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: Appropriate stability data have been presented for several full-scale batches. Based on these results, a satisfactory re-test period has been established when stored in LDPE bags (primary packaging).

4.2 Drug product

Description and composition: The drug product Yselty can be described as pale-yellow film-coated tablets with two dosage strengths: 100 mg and 200 mg linzagolix choline. The two strengths can be distinguished by the engraved number.

Manufacture: Linzagolix film-coated tablets are manufactured by granulation followed by lubrication, compression, film-coating. Tablets are then packaged into blisters through an automated process.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance (visual examination), identity (UV, HPLC), assay (HPLC), uniformity of dosage units, degradation products (HPLC), water content, dissolution and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Container closure system: The drug product is packaged into PVC/PVDC-Alu blisters. The blisters are packed in a cardboard box as secondary packaging.

Stability: Appropriate stability data have been generated for the drug product in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Yselty containing the new active substance linzagolix choline, the Nonclinical Assessment Division at Swissmedic conducted an abridged evaluation, which was based on the CHMP assessment report EMEA/H/C/005442/0000 (dated 22.04.2022).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Yselty in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues, e.g. liver and reproductive toxicity that are of concern for human use, were identified in the nonclinical studies. The presented data suggest sufficient exposure margins to findings in nonclinical species. All nonclinical data that are relevant for safety are mentioned in the Information for healthcare professionals and the RMP.

There is no safety concern regarding impurities and excipients.

Based on the ERA, the risk to the environment is low.

6 Clinical aspects

6.1 Clinical pharmacology

The PK of linzagolix has been adequately studied in healthy subjects as well as the relevant patient population. Linzagolix exhibits linear and time-independent pharmacokinetics over the relevant dose range and can be administered irrespective of food intake.

Linzagolix is metabolised or excreted by several pathways. Therefore, its interaction potential as a victim drug due to inhibition of a single pathway is likely to be low. However, most inducers act on several CYPs and transporters and may well reduce the exposure and efficacy of linzagolix.

Linzagolix is a weak CYP2C8 inhibitor, which limits its concomitant use with CYP2C8 substrates with a narrow therapeutic window. However, apart from CYP2C8, the interaction potential of linzagolix as a perpetrator drug appears to be low.

Subjects with severe hepatic impairment or moderate or worse renal impairment should not be treated with linzagolix. Patients with mild renal impairment need monitoring for AEs.

The PD of linzagolix has been sufficiently characterised, and linzagolix showed the expected effects on hormone levels. However, linzagolix caused a prolongation of the QT interval, warranting a respective warning.

For details regarding the clinical pharmacology refer to the Information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

No specific dose-finding study has investigated the indication of fibroid-associated hypermenorrhoea. Such a study has only been conducted for the indication of endometriosis (EDELWEISS study). This appears acceptable as the same objective is being pursued in both cases, namely an estradiol level in a range that, on the one hand, sufficiently suppresses fibroid growth and, on the other, mitigates oestrogen deficiency symptoms and, in particular, BMD loss as far as possible. The above-mentioned study investigated doses of 50, 75, 100 and 200 mg compared to placebo. This study was conducted with linzagolix monotherapy.

However, the selection of the doses investigated in phase III and the requested doses were ultimately based on several phase II studies that also investigated the indication of endometriosis (even though these included patients who also had fibroids).

Whereas the early phase II studies found clear dose dependency for the pharmacodynamic parameters, this was less clear in the EDELWEISS study, especially with increasing duration of therapy. However, in view of a high drop-out rate, selection effects cannot be ruled out.

By contrast, clear dose dependency was found in all studies for oestrogen deficiency symptoms, particularly for hot flushes.

The uncertainties concerning dose finding were mitigated by the fact that four different dose regimens were investigated in the pivotal studies.

6.3 Efficacy

Two pivotal studies (PRIMROSE 1 and 2) were conducted to demonstrate the efficacy of the proposed product (with and without ABT). Since both studies had a largely identical design, the data were pooled. While PRIMROSE 1 was conducted exclusively in the USA, European patients were predominantly included in PRIMROSE 2.

The studies were 1:1:1:1:1 randomised, double-blind, placebo-controlled trials in which four active arms were compared with placebo. The patients were stratified by race since fibroids are more prevalent in black women and the symptoms are often more severe in this population.

Both studies had a total treatment period of 52 weeks, divided into two phases. Four different active dosage regimens were initially compared with placebo in a 24-week treatment phase: 100 mg monotherapy; 100 mg plus ABT; 200 mg monotherapy; and 200 mg plus ABT. This was followed by a second, likewise double-blind, phase lasting 28 weeks. Patients in the groups that had received 100 mg monotherapy, 100 mg plus ABT and 200 mg plus ABT continued to be treated with the same dose previously administered during the first 24 weeks. By contrast, patients in the 200 mg monotherapy group were switched to 200 mg plus ABT to avoid a clinically relevant loss of BMD.

Another factor common to both studies was a treatment-free follow-up period, during which patients were to be monitored for changes in their BMD for 24 months after discontinuation of the study medication.

The main difference between the two studies was the procedure adopted in the placebo group, due to differing requirements in Europe and the USA. Whereas all patients in the placebo group in PRIMROSE 2 were switched to 200 mg linzagolix plus ABT after 24 weeks, the FDA required placebo control throughout the entire 52-week study period. Therefore, the patients in the placebo group in PRIMROSE 1 were re-randomised 1:1 to 200 mg plus ABT or placebo after 24 weeks.

The studies enrolled premenopausal women aged 18 and over (with no upper age limit) with a BMI of ≥18 kg/m^2 and with at least one fibroid with a diameter of ≥2 cm or multiple small fibroids with a calculated uterine volume of ≥200 cm^3. During the screening phase, the presence of regular cycles had to be documented over at least two cycles. The presence of HMB also had to be confirmed during this period. To this end, the menstrual blood loss (MBL) on the first 8 days of the two screening cycles had to be >80 ml in each case.

The menstrual blood loss in both pivotal studies was determined by the alkaline haematin method.

All patients with contraindications for oestrogen therapy were excluded. Other relevant exclusion criteria were

- any gynaecological findings that could interfere with the assessment of efficacy and safety, e.g. uterine polyps >2 cm
- clinically relevant breast changes
- any surgical procedure for the fibroids within the 6 months preceding the study inclusion
- expected surgery within the next 6 months due to the severity of symptoms.
- DXA scan Z-score ≤-2

Iron therapy was permitted during the study. If the baseline Hb was less than 10g/dl, iron therapy had to be administered, and in most cases the dosage was 324 mg iron fumarate per day.

The primary endpoint of both studies was the proportion of patients with an MBL of ≤80 ml and a reduction in MBL of ≥50% compared to baseline at week 24. The last 28 days prior to the study visit were used as the basis for this endpoint.

As a result of the multiple testing (i.e. 4 active groups each versus placebo), the significance level for comparisons was specified as p=0.0125. The primary analysis (in week 24) was equivalent to an ITT analysis. Most patients also took part in the second phase of the study from week 25 to week 52, although no confirmatory tests were performed in week 52.

A statistical analysis was conducted exclusively for the four active groups compared to placebo, whereas no comparison between the various active groups was planned.

In addition, five "ranked secondary efficacy endpoints" were defined, and these were also subjected to confirmatory testing. A hierarchical approach was chosen to adjust for multiple testing. These main

secondary endpoints were (in the stated order): time to reach the response criterion, i.e. an MBL ≤80 ml and a reduction of ≥50% from baseline; amenorrhoea rate; time to reach amenorrhoea; number of bleeding days in the last 28-day interval before week 24; Hb in the subgroup of patients who had anaemia at baseline. Numerous other secondary endpoints were also defined, but these were not subjected to confirmatory testing (e.g. fibroid and uterine volume and health questionnaires).

A total of n=574 patients were randomised in PRIMROSE 1 compared to n=535 patients in PRIMROSE 2.

Drop-out rates differed considerably between the two studies. In PRIMROSE 1 only 68% of the patients completed the study up to week 24, whereas in PRIMROSE 2 this proportion was much higher at 85%. The most common reason for discontinuation in both studies was "subject's request".

In the PRIMROSE 1 study, 22% of the patients showed major protocol violations, compared to 15% in PRIMROSE 2. These patients were not included in the PP population.

The demographic and baseline characteristics were balanced between the treatment groups in both studies, although certain differences were apparent between the two studies due to the different geographical regions.

Average age was 41-43 years. The average BMI in PRIMROSE 1was 32-33 kg/m^2 and approx. 27 kg/m^2in PRIMROSE 2.

The baseline MBL in PRIMROSE 1 was comparable in all treatment groups at approx. 200 ml. In PRIMROSE 2, it was higher overall and showed higher variability between treatment groups, with values ranging from 193 ml to 245 ml.

A clear difference between the two studies was evident for baseline Hb, which was lower in PRIMROSE 1, at an average of 10.5-11 g/dl, compared to 11.5 g/dl in PRIMROSE 2. However, there were no differences between the treatment groups within either study.

Overall, the study population appeared sufficiently representative of a population of patients with symptomatic fibroids.

In both studies, statistically significant superiority versus placebo was shown for the primary endpoint in all active groups. The findings for the primary endpoint were consistent in both studies, although the response rates tended to be slightly higher in PRIMROSE 2. The highest response rate was found in the 200 mg plus ABT group in both studies. The combination of linzagolix with ABT did not result in a reduction in efficacy.

According to the pooled data from both studies, the response rates were 56.5% for the 100 mg monotherapy, 71.6% for 100 mg plus ABT, and 84.5% for 200 mg plus ABT, compared to 32.2% for placebo.

The findings for the PP population and the sensitivity analyses were consistent with the primary analysis.

The onset of effect was rapid in all cases, with a significant and clinically relevant reduction in MBL already apparent in the first 4 weeks (i.e. in the first cycle of therapy).

The findings for the 5 main secondary endpoints were consistent with those for the primary endpoint.

Overall, a benefit compared to placebo was demonstrated for all investigated dosage regimens. On the one hand, a dose-response relationship was apparent and, on the other, there was no evidence to indicate that the addition of ABT would lead to a relevant loss of efficacy.

Estradiol levels mainly remained within the target range of 20-60 pg/ml for treatment groups with ABT and also for the monotherapy with 100 mg.

Overall, both pivotal studies proved that linzagolix was effective in treating fibroid-associated HMB.

Efficacy was maintained to week 52.

Efficacy data for a treatment period of more than 12 months and data on the course of MBL after discontinuation of treatment were not collected.

6.4 Safety

For the safety analysis, the data from the two pivotal studies were pooled, with the assessment of data up to week 24 on the one hand and up to week 52 on the other. Data from n=1037 patients were available for the analysis after 24 weeks and from n=757 patients after 52 weeks. In addition, the safety findings from the EDELWEISS dose-finding study (for endometriosis) were also taken into account. Overall, the data available for the assessment of short-term safety, i.e. up to a treatment period of one year, can be considered sufficient.

The observed safety profile was consistent with what would be expected for a GnRH antagonist (with or without ABT). No new, unexpected safety signals were observed.

In the data up to week 24, the overall incidence of AEs in the active treatment groups was slightly higher than in the placebo group. Within the active groups, there was slight dose dependency as well as a slightly higher incidence with monotherapy compared to the corresponding combination.

The most common AEs were hot flushes, headaches and anaemia. As expected, hot flushes showed clear dose dependency, with a significantly higher incidence with monotherapy compared to the combination with ABT.

SAEs were rare overall and, in the vast majority of cases, showed no causal relationship with the study medication.

Treatment was discontinued due to AEs in 8% of patients.

In the second six months of the treatment period, the safety profile was essentially the same as that observed up to week 24.

The endometrial safety of the product (including in combination with ABT) was confirmed by endometrial biopsies.

Special safety aspects

As would be expected especially during monotherapy with a GnRH antagonist, the risk of bone mineral density (BMD) loss must be deemed particularly relevant. Therefore, the effect of linzagolix, with or without ABT, on the course of bone density, particularly in the lumbar spine and hip, was comprehensively investigated in all phase II/III studies. A follow-up study was also conducted to monitor bone density over a period of up to 24 months after discontinuation of linzagolix.

Overall, the applicant investigated the effects on BMD carefully also to identify differences between monotherapy and the combination with ABT, i.e. to confirm the benefit of the add-back therapy.

Here too, the findings were consistent with what is already known for the class of GnRH antagonists. There was a dose-dependent loss of BMD, which was mitigated by the use of ABT. In most cases, the loss was ≤3%, which is within the range of variability of the DXA scan findings. A BMD loss >8% occurred only in a few isolated cases.

However, it should be emphasised that data are currently available only for a maximum treatment period of 12 months. The follow-up data after discontinuation of linzagolix are also limited, as only n=130 patients were included in the 24-month follow-up.

In any case, careful monitoring is needed so that patients with "above-average" or progressive BMD loss can be identified at an early stage and treatment is discontinued if deemed necessary.

It should also be noted that, in addition to existing osteoporosis or other types of metabolic bone disease, all risk factors for BMD loss constituted an exclusion criterion in the clinical trials. Consequently, it is not possible to assess a possible bone risk for at-risk patients.

Increased transaminase levels are known to occur with GnRH antagonists, however, for linzagolix, findings were in line with what would be expected.

6.5 Final clinical benefit risk assessment

Fibroids are benign, hormone-sensitive, soft tissue tumours of the uterus, whose growth is stimulated particularly by oestrogens. They have a high prevalence and increase during the course of the fertile phase of life.

Most fibroids are asymptomatic but around a quarter of affected women develop symptoms that require treatment. The primary problem is heavy menstrual bleeding (HMB), which can lead to iron deficiency and anaemia.

Yselty contains the GnRH antagonist linzagolix, which can be administered with or without ABT.

Beneficial effects

The efficacy of linzagolix with or without ABT in treating heavy menstrual bleeding with fibroids was demonstrated in two pivotal studies. In anaemic patients, the reduction in MBL was also associated with a rise in Hb.

The effects observed for all four investigated dosage regimens were statistically significant and can be considered clinically relevant.

Efficacy was maintained until week 52. No data are available for a treatment period lasting more than 12 months.

Since fibroids with a diameter >12 cm constituted an exclusion criterion, no data are available for patients with fibroids of this size.

Unfavourable effects

The safety profile observed for linzagolix largely corresponded with what would be expected of this kind of hormonal therapy. No new, unexpected safety signals were observed.

Uncertainties exist particularly as regards long-term safety, especially for BMD.

However, the data available to date indicate that

- the risk of BMD loss can be substantially mitigated by the addition of ABT
- at least partial recovery of the BMD occurs after discontinuation of the treatment

What cannot be assessed however is the risk of a (further) BMD loss in patients who already have risk factors for osteoporosis, since such patients were excluded from taking part in the studies.

A PASS study is already being planned to obtain further BMD data.

Benefit-risk balance

Overall, the benefit-risk balance was assessed to be positive for linzagolix as 100mg monotherapy, 100mg plus ABT and 200mg plus ABT.

DXA scans every two years should are recommended. A trial withdrawal should also take place every two years in premenopausal patients so that the onset of the menopause can be identified and the preparation then discontinued in order to prevent patients from being exposed to any unnecessary risk of BMD loss.

When linzagolix is used in combination with ABT, the size of fibroids should be monitored at least every two years in younger patients so that any (ABT-induced) fibroid growth is detected.

Since contraceptive efficacy has not been demonstrated for linzagolix, effective non-hormonal contraception should be used during therapy if applicable

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Yselty was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Yselty, film-coated tablets

Composition

Active substances

Linzagolix (as choline salt)

Excipients

Tablet core

Lactose monohydrate (125.7 mg or 251.4 mg), microcrystalline cellulose (E 460), low-substituted hydroxypropylcellulose (E 463a), hydroxypropylcellulose (E 463), croscarmellose sodium (E 468) (corresponding to max. 1.8 mg or max. 3.6 mg sodium), magnesium stearate

Film coating

Macrogol-poly(vinyl alcohol) grafted copolymer (E1209), talc (E 553b), titanium dioxide (E 171), iron (III) hydroxide oxide hydrate (E172)

Pharmaceutical form and active substance quantity per unit

Film-coated tablet (tablet).

Yselty 100 mg film-coated tablets

Each film-coated tablet contains 100 mg linzagolix as choline salt.
Round, pale yellow film-coated tablets with a diameter of 10 mm, embossed with “100” on one side and smooth on the other.

Yselty 200 mg film-coated tablets

Each film-coated tablet contains 200 mg linzagolix as choline salt.
White, pale yellow film-coated tablets with dimensions of 19 mm to 9 mm, embossed with “200” on one side and smooth on the other.

Indications/Uses

Treatment of hypermenorrhoea associated with fibroids in adult women before the onset of menopause.

A bone density measurement must be carried out with dual X-ray absorptiometry (DXA scan) before starting treatment with Yselty in patients with risk factors for osteoporosis or bone density loss (see “Warnings and precautions”).

Dosage/Administration

Treatment with Yselty should be initiated and monitored by a doctor experienced in the diagnosis and treatment of fibroids.
Pregnancy must be ruled out before starting treatment with Yselty.

Usual dosage:

- The recommended dosage is 100 mg together with an add-back therapy (ABT; 1 mg oestradiol plus 0.5 mg norethisterone acetate) once daily. If this is not effective enough, then the dose can be increased to 200 mg linzagolix together with the add-back therapy (1 mg oestradiol plus 0.5 mg norethisterone acetate) once daily.
- 100 mg once daily in patients in whom exogenous administration of oestrogen is contraindicated or needs to be avoided.
- 200 mg once daily for short-term use (< 6 months) in patients in whom exogenous administration of oestrogen is contraindicated or needs to be avoided, if it must be assumed that the therapeutic objective cannot be achieved with 100 mg.
  Due to the risk of a decrease in bone mineral density (BMD) with prolonged use, the 200 mg dose should be prescribed for no longer than 6 months without concomitant ABT.

Starting treatment

Treatment with Yselty should preferably be started in the first week of the menstrual cycle.

Duration of treatment

Yselty is taken continuously once a day. A DXA scan is recommended after the first year of treatment as safety data, in particular data on the course of bone density, are only available for a treatment duration of up to 12 months (see “Warnings and precautions”).

If therapy is continued beyond a period of 12 months, the course of BMD should be monitored at two-yearly intervals using a DXA scan. If linzagolix is used in combination with add-back therapy, the size of the fibroid(s) should also be monitored in accordance with standard clinical practice, but at least every two years.
Premenopausal patients should also undergo a treatment-free trial every two years. Treatment should be discontinued after the onset of menopause.

Forgotten dose

If a dose is forgotten, it should be taken as soon as possible. Treatment is then continued the next day at the usual time.

Method of administration

To be taken orally.
Yselty can be taken with or without food (see “Pharmacokinetics”).
The 200 mg dose can be taken either as one 200 mg tablet or as two 100 mg tablets.

Special dosage instructions

Paediatric population

Yselty is not indicated for use in children and adolescents and no paediatric data are available for the preparation.

Elderly patients

Yselty was studied exclusively in premenopausal patients. There is generally no indication in postmenopausal women, as fibroids regress spontaneously after menopause.

Patients with hepatic disorders

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Yselty is contraindicated in severe hepatic impairment (Child-Pugh class C) (see “Pharmacokinetics”).

Patients with renal disorders

The use of Yselty should be avoided in cases of moderate (eGFR = 30-59 ml/min) or severe renal impairment (eGFR < 30 ml/min) as well as in terminal renal failure (see “Pharmacokinetics”).
No dose adjustment is required for mild renal impairment (eGFR = 60-89 ml/min). However, patients should be monitored for possible adverse reactions.

Contraindications

- Known osteoporosis
- Genital bleeding of unknown aetiology
- Severe hepatic impairment (Child-Pugh C)
- Pregnancy or breast-feeding (see section “Pregnancy, lactation”)
- Simultaneous use of hormonal contraceptives
- Hypersensitivity to the active substance or to any of the excipients

If an ABT is administered at the same time, the contraindications for the corresponding preparation must also be observed.

Warnings and precautions

A complete medical history (including family history) must be taken before initiating or resuming treatment with Yselty. Blood pressure must be measured and a physical examination must be carried out, guided by the contraindications (see “Contraindications”) and warnings. During treatment, regular checks should be carried out in accordance with standard clinical practice.

Pregnancy must be ruled out before starting or resuming treatment. In addition, hormonal contraceptives must be discontinued before starting treatment with Yselty. Non-hormonal contraceptive methods should be used during therapy and for at least 1 month after discontinuation of Yselty (see also “Pregnancy, lactation”). The patient should be advised on a suitable contraceptive method.

Effects on bone mineral density (BMD)

The effects of linzagolix on BMD were analysed using a DXA scan. Dose- and time-dependent changes in BMD were observed in both pivotal studies (see “Properties/Effects”). The BMD loss was attenuated by concomitant ABT.
Changes in BMD were most pronounced under monotherapy with 200 mg linzagolix. After 6 months of treatment, a mean reduction in BMD in the lumbar spine (LS) of > 3 % and > 8 % was observed in 55 % and 4 % of patients, respectively, compared to baseline using this dosing regimen.
After 12 months of treatment with linzagolix 100 mg, linzagolix 100 mg with ABT or linzagolix 200 mg with ABT, a mean reduction in BMD in the lumbar spine of > 3 % and > 8 % was observed in 38 % and 7 %, 16 % and 0 %, and 27 % and 1 % of patients, respectively, compared to baseline.
The course of BMD was also investigated after discontinuation of linzagolix. All treatment groups showed at least partial recovery of BMD 6 months after the end of treatment.
The effects on BMD can be mitigated by combining linzagolix with ABT. However, it should be noted that the efficacy of oestradiol may be reduced and protection against BMD loss may be impaired in cases of co-medication with CYP3A4 inducers.

Patients with risk factors for osteoporosis or other metabolic bone diseases (such as low body weight, chronic alcohol and/or tobacco consumption, family history of osteoporosis) were excluded from the studies. Patients with such risk factors and co-medication that may have an unfavourable effect on BMD (e.g. systemic corticosteroids, anticonvulsants) should therefore undergo a particularly careful risk-benefit assessment. In such cases, a DXA scan must be performed before starting treatment with Yselty. Therapy with Yselty should not be initiated or continued if the risk associated with BMD loss exceeds the potential benefit of treatment.

A DXA scan is recommended after a treatment period of 1 year to rule out a more severe loss of BMD. Thereafter, a further DXA scan is recommended every two years.

There is no adequate definition of when the treatment-induced BMD loss in this population should be considered clinically relevant. However, in the event of a BMD loss of ≥ 3 %, the patient concerned should be closely monitored and the risk-benefit ratio of continuing treatment should be weighed up on an individual basis. The patient's age and general risk of osteoporosis, as well as the baseline BMD value, should be considered.

A possible influence of vitamin D on the course of BMD was not investigated. Nevertheless, ensuring an adequate intake of vitamin D and calcium is recommended during treatment with Yselty.

QT prolongation

Linzagolix leads to a slight prolongation of the QT interval (see “Properties/Effects”). However,there have been no indications to date of a risk of clinically relevant QT prolongation or torsades de pointes. Caution should be exercised in patients with risk factors for QT prolongation, such as known cardiovascular disease, congenital or acquired QT prolongation or hypokalaemia, as well as for the concomitant use of drugs known to prolong the QT interval (e.g. azole antimycotics, Class IA or III anti-arrhythmics, certain psychotropic drugs). Particular caution is also required in patients with concomitant diseases that can lead to increased linzagolix plasma concentrations (see “Pharmacokinetics”).

Effects of linzagolix on hepatic function

Asymptomatic, transient increases in liver enzymes (particularly alanine aminotransferase, ALT, and aspartate aminotransferase, AST) have been reported during the use of linzagolix (see “Undesirable effects”). The incidence of such changes was < 3 % and showed dose dependency, especially in cases with a greater increase. An increase in transaminases to at least 3 times the upper limit of normal (ULN) was found in around 1 % of the study participants. There were no cases of a simultaneous increase in bilirubin.
Patients should be instructed to consult a doctor immediately if there are any signs of liver damage, such as nausea, vomiting or jaundice. If changes in liver enzymes occur during the use of Yselty, treatment should be interrupted until the liver values have returned to normal. Treatment should be discontinued if jaundice develops.

Patients with abnormal liver function parameters (≥ 2 times the upper limit of normal, ULN) were excluded from the studies conducted with linzagolix. Yselty should therefore only be used with caution in patients with a history of hepatic disorders. In these cases, liver function must be monitored regularly during treatment (including a determination of liver enzymes before starting treatment). Yselty is contraindicated in severe hepatic insufficiency (Child-Pugh C).

Depressive disorders and suicidality

Depression and depressive moods are known to be potential adverse reactions to treatment with sex hormones. Cases of mood swings (in up to 2 % of patients) and, less commonly, depressive disorders, were also observed during treatment with linzagolix. Such disorders may occur early on, shortly after starting treatment. A depression can take a serious course and constitutes a risk factor for suicide or suicidal behaviour. Patients should therefore be informed on the possible symptoms of depressive disorders. It is essential that the user is advised to contact a doctor immediately if she notices any mood swings or other symptoms of depression when using Yselty.
Patients with a history of depression must be carefully monitored. Yselty should be discontinued if serious depression recurs.

Change in the bleeding pattern

Bleeding disorders (such as metrorrhagia, menorrhagia or menometrorrhagia) were reported in the pivotal studies during treatment with linzagolix. Bleeding disorders were reported slightly more frequently in the two groups with ABT than in the groups without ABT.
The patient should be made aware that treatment with linzagolix generally leads to weaker menstrual bleeding and often to amenorrhoea. Irregular bleeding is also possible, especially at the start of treatment. The doctor should be contacted in the event of persistent excessive bleeding.

Contraception

No contraceptive efficacy has been demonstrated for linzagolix. Patients at risk of pregnancy must use a reliable non-hormonal contraceptive method during treatment with Yselty (see “Pregnancy, lactation”).

Recognising pregnancy is more difficult

The intensity of menstrual bleeding is usually reduced during treatment with linzagolix, and a high proportion of patients experience amenorrhoea. This can make it difficult to recognise pregnancy at an early stage. A pregnancy test must be carried out if pregnancy is suspected. Treatment must be discontinued if pregnancy is confirmed (see “Contraindications” and “Pregnancy, lactation”).

Effects of linzagolix on lipid levels

Increases in lipid levels have been observed during treatment with linzagolix (see “Undesirable effects”). These changes were generally not clinically relevant. However, monitoring of serum lipids is recommended for patients with pre-existing lipid metabolism disorders.

Alopecia

Hair loss and alopecia have been reported during the use of oral GnRH antagonists. This was not a specific pattern of alopecia, and the adverse effect did not lead to discontinuation of the study in most

cases. Nothing is known about the reversibility of such alopecia. Discontinuation of treatment should be considered if clinically relevant hair loss occurs during the use of Yselty.

Concomitant use with other treatments for uterine fibroids

No data are available on the concomitant use of linzagolix with other medicinal products for the treatment of fibroid-associated hypermenorrhoea (such as progestogens or GnRH analogues). Such combinations are therefore not recommended.
Yselty must not be used in patients with hormone receptor-positive breast cancer who are receiving oestrogen-suppressing therapy (e.g. with aromatase inhibitors, tamoxifen or GnRH analogues).

Patients with hepatic disorders

An increase in the mean unbound exposure to linzagolix by a factor of 2-3 was reported in patients with severe hepatic impairment (Child-Pugh class C). Potential resultant safety risks can thus not be ruled out. Yselty must therefore not be used in patients with severe hepatic insufficiency (see “Contraindications”).
No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B) (see “Dosage/Administration” and “Pharmacokinetics”).

Patients with renal disorders

Yselty should not be used in patients with moderate (eGFR = 30-59 ml/min) or severe renal impairment (eGFR < 30 ml/min) and in patients with terminal renal failure (see “Dosage/Administration”). No dose adjustment is necessary in patients with mild renal impairment (eGFR = 60-89 ml/min). However, patients should be monitored for possible adverse reactions (see “Pharmacokinetics”).

Interactions with CYP2C8 substrates

The use of Yselty should be avoided in patients using drugs with a narrow therapeutic margin that are also CYP2C8-sensitive substrates (e.g. paclitaxel, sorafenib or repaglinide, see “Interactions”). Monitoring for adverse reactions is recommended when Yselty is used concomitantly with other CYP2C8 substrates.

Warnings and precautions regarding an ABT

If an ABT is prescribed at the same time, the Information for Healthcare Professionals for the corresponding preparation must also be consulted and all warnings and precautions contained therein must be observed.

Excipients of particular interest

Lactose: Yselty contains lactose. Patients with the rare hereditary galactose intolerance, complete 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, i.e. it is almost "sodium-free".

Interactions

Pharmacokinetic interactions

Effects of other substances on the pharmacokinetics of linzagolix

OATP1B1 and OATP1B3 inhibitors:

In vitro, linzagolix is a substrate for the organic anion transporting polypeptides (OATP) 1B1 and OATP1B3, which are involved in the hepatic uptake of drugs, suggesting that they may play an important role in the excretion of linzagolix. The effects of rifampicin, an inhibitor of OATP1B1 and OATP1B3, on exposure to linzagolix was investigated in an interaction study. When linzagolix and rifampicin were administered concomitantly, C_{max} and AUC were slightly increased (1.1- to 1.2-fold increase), but this increase is not considered clinically relevant. No clinically relevant interactions between linzagolix and OATP1B1 / OATP1B3 inhibitors are therefore to be expected.

OAT3 inhibitors:

In vitro, linzagolix is a substrate for the organic anion transporter 3 (OAT3), which is involved in the renal excretion of drugs. However, the effects of an OAT3 inhibitor on exposure to linzagolix have not been investigated in a clinical trial.

CYP enzyme inducers:

The effects of CYP inducers on exposure to linzagolix have not been investigated. However, concomitant administration can lead to reduced exposure to linzagolix and thus to reduced efficacy.

Effects of linzagolix on the pharmacokinetics of other substances

CYP2C8 substrates:

Linzagolix is a weak CYP2C8 inhibitor (see Table 1). Concomitant use with CYP2C8 substrates with a narrow therapeutic margin should be avoided.

Other interactions

Based on clinical interaction studies, no relevant interactions between linzagolix and substrates for CYP3A4, OAT3 and OATP1B1 are to be expected (see Table 1).
Table 1 shows the geometric mean ratio (GMR) for the pharmacokinetic parameters for administration with/without concomitant medication with 90 % confidence intervals (CI)

Table 1: Interactions between linzagolix and other medicinal products

Active substance (dose)	Effect on active substance concentration GMR (90 % CI)	Recommendations for concomitant intake

	(possible interaction mechanism)	
Repaglinide (0.5 mg single dose) Linzagolix (200 mg once daily, 6 days)	Repaglinide AUC_{0-t}: 1.949 (1.811; 2.097) C_{max}: 1.278 (1.093; 1.494) **(CYP2C8 inhibition)**	Avoid concomitant use with CYP2C8 substrates with a narrow therapeutic margin (e.g. paclitaxel, sorafenib or repaglinide) (see “Warnings and precautions”)
Midazolam (2 mg single dose), Linzagolix (200 mg, once daily, 7 days)	Midazolam AUC 1.0226 (0.9635; 1.0853) C_{max}: 0.9927 (0.9261; 1.0641) 1-OH metabolite AUC: 1.0851 (1.0347; 1.1381) C_{max}: 1.0939 (0.9888; 1.2100) No clinically relevant interaction to be expected **(CYP3A4 induction)**	No dose adjustment necessary
Benzylpenicillin (600 mg, single dose i.m.) Linzagolix (200 mg single dose)	Benzylpenicillin AUC: 1.043 (1.013; 1.074) C_{max}: 0.962 (0.842; 1.099) No clinically relevant interaction to be expected **(OAT3 inhibition)**	No dose adjustment necessary
Pitavastatin (1 mg, single dose) Linzagolix (200 mg single dose)	Pitavastatin AUC: 1.094 (1.037; 1.154) C_{max}: 1.212 (1.014; 1.448) No clinically relevant interaction to be expected **(OATP1B1 inhibition)**	No dose adjustment necessary

Pregnancy, lactation

Women of child-bearing age

No contraceptive efficacy has been demonstrated for linzagolix. Women who could become pregnant must use a reliable non-hormonal contraceptive method during treatment with Yselty.

Pregnancy

Yselty is contraindicated during pregnancy. Pregnancy must be ruled out before starting to use this medicine. Treatment must be discontinued if pregnancy occurs or is suspected during the use of Yselty.
There are no or only limited data available on the use of linzagolix in pregnant women. Due to the pharmacological effects, undesirable effects on pregnancy cannot be ruled out. In animal studies, exposure to linzagolix early on in gestation increased the risk of early pregnancy loss (see “Preclinical data”).

Lactation

It is not known whether linzagolix or its metabolites are excreted in human breast milk. In animal studies, linzagolix passed into the milk. A risk to the breast-feeding infant cannot be ruled out. Yselty is therefore contraindicated during breast-feeding.

Fertility

No data are available on the possible effects of linzagolix on human fertility. Animal studies (see “Preclinical data”) and the mechanism of action for linzagolix indicate that fertility may be impaired during the intake of linzagolix.

Effects on ability to drive and use machines

No corresponding studies have been performed. However, linzagolix probably has no more than a negligible influence on the ability to drive and use machines.

Undesirable effects

The information on adverse reactions is based on the pooled data of the two pivotal studies, in which a total of n = 828 patients with uterine fibroids were exposed to linzagolix for a maximum of 12 months.

The most common adverse reactions were hot flushes (up to 33 %) and headaches (up to 12 %). These were dose-dependent and were also reported less commonly (as were other symptoms of oestrogen deficiency, such as vulvovaginal dryness or loss of BMD) during concomitant use with an ABT than for linzagolix alone.
Conversely, bleeding disorders were reported slightly more commonly in the treatment groups with an ABT than for monotherapy with linzagolix.

The adverse reactions are arranged according to MedDRA system organ classes and frequencies based on the following convention:
“very common” (≥1/10)
“common” (≥1/100, <1/10)
“uncommon” (≥1/1000, <1/100)
“rare” (≥1/10,000, <1/1000)
“very rare” (<1/10,000)

Metabolism and nutrition disorders

Common: Increase in total cholesterol, LDL, HDL or triglycerides (especially under monotherapy with linzagolix)

Psychiatric disorders

Common: Reduced libido, mood disorders such as mood swings, affect lability, emotional disorders, depressed mood, anxiety, depression or irritability

Nervous system disorders

Very common: Headaches (up to 12 % of patients receiving monotherapy with linzagolix)

Vascular disorders

Very common: Hot flushes (up to 33 % of patients receiving monotherapy with linzagolix)
Common: Hypertension

Gastrointestinal disorders

Common: Abdominal pain, nausea/vomiting, constipation

Hepatobiliary disorders

Common: Elevated liver enzymes

Skin and subcutaneous tissue disorders

Common: Hyperhidrosis

Musculoskeletal and connective tissue disorders

Common: Arthralgia, reduced BMD (see “Warnings and precautions”)

Reproductive system and breast disorders

Common: Bleeding disorders (e.g. menorrhagia, metrorrhagia, menometrorrhagia), lower abdominal pain

Uncommon: Vulvovaginal dryness

General disorders and administration site conditions

Common: Night sweats, asthenia

Description of specific adverse reactions and additional information

Changes in serum lipids

Fasting lipid levels (total cholesterol, LDL, HDL and triglycerides) were measured in the pivotal studies during treatment with linzagolix at three-month intervals and up to 3 months after the end of treatment. There were cases with an increase in LDL, HDL and/or triglycerides (which was generally < 15 % for LDL and < 20 % for triglycerides) in all linzagolix groups. The increase in serum lipids was greater under linzagolix monotherapy than with the additional intake of ABT. These changes were apparent from week 12 onwards and the lipid parameters had generally stabilised after 52 weeks of treatment. There were indications of a decrease in lipid levels 12 weeks after discontinuing linzagolix, but the values were still slightly elevated compared to the baseline values before the start of therapy (see “Warnings and precautions”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

There is no specific antidote. In the event of an overdose, the patient should be closely monitored and symptomatic and supportive therapy should be administered if necessary.

Properties/Effects

ATC Code

H01CC04.

Mechanism of action

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

Pharmacodynamics

Linzagolix leads to a dose-dependent suppression of the luteinising hormone and the follicle-stimulating hormone, which results in a reduction in the concentrations of oestradiol and progesterone in the blood.
Monotherapy with 200 mg linzagolix resulted in complete suppression of oestradiol concentrations into the postmenopausal range, with a median < 20 pg/ml. Conversely, median serum oestradiol concentrations in the other treatment groups (i.e. 100 mg monotherapy, 100 mg with ABT and 200 mg with ABT) were between 27 pg/ml and 48 pg/ml. Progesterone levels remained at ≤ 3.1 ng/ml in the majority of patients.
The oestradiol concentration should be in a range of 20-60 pg/ml to ensure acceptable bone safety of the therapy with sufficient effectiveness against hypermenorrhoea. After 52 weeks of treatment, the oestradiol concentration was within this target range in 32 % of patients under 100 mg linzagolix, in 42 % under 100 mg with ABT and in 52 % under 200 mg with ABT.
Safety pharmacology

QT interval

The effect of a single dose of linzagolix on the QTc interval was investigated in a randomised, open-label, placebo and positive-controlled crossover study. 48 healthy women received a dose of 200 mg linzagolix (therapeutic exposure), a dose of 700 mg linzagolix (supratherapeutic exposure), a dose of 400 mg moxifloxacin (positive control) or placebo with an appropriate washout period. Linzagolix 200 mg and 700 mg were found to have an effect on prolongation of the QT interval corrected for heart rate, with the maximum mean value observed 3 hours after the dose being 8.34 ms (90 % CI 6.44-10.23) and 9.92 ms (90 % CI 8.03-11.81), respectively.
The highest expected steady-state concentration in the QT study was estimated in healthy volunteers, whereby increases in exposure to unbound linzagolix due to pre-existing medical conditions were not considered (see “Pharmacokinetics”).

Effects on bone mineral density (BMD)

The effect of linzagolix on BMD was assessed in the two pivotal studies with a DXA scan at the start of the study, during treatment (weeks 24 and 52) and 6 months after the end of treatment. Patients with a known history of osteoporosis, other metabolic bone diseases or with risk factors for osteoporosis were excluded from participation in the study. The same applied to patients who had a Z-score ≤ -2 in the baseline examination.

Treatment with linzagolix resulted in a dose-dependent decrease in BMD, which was attenuated in each case by concomitant ABT. The greatest decrease in BMD at week 24 was in those patients who had received monotherapy with 200 mg linzagolix (-3.70 %). Conversely, the average decrease was less than 2 % in the other dose groups. Monotherapy with 200 mg was only administered until week 24 (i.e. for a maximum of 6 months), while the patients afterwards additionally received ABT until the end of the study at week 52.
There was only a slight further decrease in BMD after week 24.
BMD data are only available for a treatment duration of up to 12 months.

Effects on the endometrium

In both pivotal studies, endometrial biopsies were performed on a subgroup of patients after 24 and 52 weeks. Data after 52 weeks of treatment with linzagolix are available for n = 151 patients. The results did not raise any safety concerns (neither for linzagolix monotherapy nor for the combination with ABT).

Clinical efficacy

The efficacy of linzagolix was investigated in two randomised, double-blind, placebo-controlled phase III studies with a largely identical design (PRIMROSE 1 and PRIMROSE 2). The two studies included 511 and 501 patients. PRIMROSE 1 was carried out in the USA, PRIMROSE 2 mainly in Central and Eastern Europe. The studies had a 52-week double-blind treatment phase, followed by a 24-week treatment-free follow-up.
There are no data on the efficacy and safety of linzagolix for a treatment duration of more than 12 months.

Patients aged 18 years and older with heavy menstrual bleeding (menstrual blood loss [MBL]/cycle > 80 ml) associated with uterine fibroids were included. As a prerequisite for inclusion in the studies, the presence of at least one fibroid with a diameter ≥ 2 cm had to be confirmed sonographically. However, fibroids with a diameter > 12 cm were an exclusion criterion. The MBL was determined using the alkaline haematin method.

The patients were randomised 1:1:1:1:1 and initially received one of the following treatments for 6 months: placebo, linzagolix 100 mg, linzagolix 200 mg, linzagolix 100 mg with concomitant ABT (1 mg oestradiol / 0.5 mg norethisterone acetate, “with ABT”) or linzagolix 200 mg with ABT, each once daily. After 24 weeks, the patients in the placebo group and the 200 mg monotherapy group were each switched to linzagolix 200 mg with ABT (except in PRIMROSE 1, in which half of the placebo patients remained on placebo until week 52). All other patients continued treatment with the same dose that they had already received up to week 24.

The mean age of the patients was 42 years (range: 20 to 58 years), mean body mass index was 29.9 kg/m^2 (range: 16-58.6 kg/m^2). About 63.5 % of the women were White, 34.5 % Black and 2 % belonged to other ethnicities.
The primary efficacy endpoint was a response, defined as an MBL of ≤ 80 ml in the last 28 days before week 24, with a simultaneous reduction of ≥ 50 % compared to the baseline value. In addition, five secondary endpoints were also subjected to confirmatory testing, including the course for Hb levels in anaemic patients. Health questionnaires were also used as secondary endpoints.

A statistically significantly higher response rate was shown for all four dosing regimens at week 24 compared to placebo (Table 2).

Table 2 Responders (patients with reduced menstrual blood loss) at week 24

Study	PRIMROSE				
Treatment	Placebo	Yselty			
		100 mg	100 mg + ABT	200 mg	200 mg + ABT
N	205	191	208	208	200
Percentage (95 % CI) of responders[1, 2]	32.2 (25.9, 39.1)	56.5 (49.2, 63.7)	71.6 (65.0, 77.7)	74.5 (68.0, 80.3)	84.5 (78.7, 89.2)

[2] Clopper-Pearson 95 % CI, p-values ≤ 0.003 for the odds ratio versus placebo (Cochran-Mantel-Haenszel test with stratification by ethnicity).
ABT: oestradiol 1 mg/norethisterone acetate 0.5 mg

A reduction in MBL was already achieved within the first 4 weeks of treatment and was then maintained until week 52.

The amenorrhoea rate at week 24 was statistically significantly higher in all dose groups than under placebo and was between 34 and 81 %. As for the primary endpoint, a dose-response relationship was also found here.
There was an increase in Hb concentrations by week 24 in patients with a baseline Hb < 12 g/dl, which also showed a dose-response relationship.
The monotherapy with 100 mg linzagolix also performed more poorly numerically than the two dosing regimens with ABT in the confirmatory secondary endpoints. As for the primary endpoint, the efficacy was maintained until week 52 in relation to these endpoints.
The findings for the other secondary endpoints (including those for the health questionnaires) were also consistent with those for the primary endpoint.

A statistically significant reduction in uterine and fibroid volume (by 39 % and 48 %, respectively) compared to placebo was found exclusively for 200 mg linzagolix without ABT at week 24. After the addition of ABT after week 24, the volume increased back to the baseline level.

Pharmacokinetics

Absorption

Linzagolix was rapidly absorbed after oral administration of a single dose of 100 mg or 200 mg, reaching C_{max} approximately 2 hours after administration. Linzagolix showed dose-linear pharmacokinetics and no relevant accumulation at steady-state in a dose range from 12.5 mg to 400 mg.

The use of linzagolix (200 mg) with a high-fat meal appeared to delay and slightly decrease peak plasma concentrations, which appeared to be consistent with delayed gastric emptying after the high-fat meal. However, this had no effect on the extent of exposure and is not considered clinically relevant.

Distribution

Linzagolix is strongly bound (> 99 %) to plasma proteins, especially albumin. There was no distribution into the erythrocytes. The volume of distribution (Vd/F) after 7 consecutive days of oral administration of 100 mg or 200 mg linzagolix was 11,067 litres (CV: 20.4 %) and 11,178 litres (CV: 11.8 %).

Metabolism

In vitro studies show that linzagolix is mainly metabolised by CYP2C9, CYP2C8 and CYP3A4. Up to 7 metabolites were quantified in plasma, urine and faeces as part of producing a metabolite profile and to identify linzagolix. The predominant component in the human plasma profiles was unchanged linzagolix. Similarly, linzagolix was the predominant component in the urine and one of the main components in the faeces. All metabolites in the plasma were present at less than 10 % of the total exposure associated with linzagolix.

Elimination

The half-life of linzagolix was about 15 hours after multiple doses. After administration of a ^{14}C-labelled dose, 52 % of linzagolix was excreted in the urine and 38 % in the faeces. After administration of several doses of 100 mg and 200 mg, the geometric mean apparent clearance (CL/F) of linzagolix was 0.522 l/h (CV: 20.1 %) and 0.499 l/h (CV: 15.2 %), respectively.

Kinetics in specific patient groups

The population pharmacokinetic analysis showed that the CL/F was reduced by 22.5 % in Black study participants compared to Caucasian study participants and that age had no relevant influence on the CL/F.

Body weight (BW)

BW was found to influence the linzagolix PK based on the population pharmacokinetic analysis. The CL/F was predicted to be about 19.2 % lower in patients with a BW of 52.7 kg (5th percentile), and around 42 % higher in patients with a body weight of 112 kg (95th percentile) than in patients with a body weight of 70 kg.

Patients with hepatic disorders

A clinical study in patients with hepatic impairment (mild: Child-Pugh class A, moderate: Child-Pugh class B and severe: Child-Pugh C) showed no relevant effects on total plasma exposure to linzagolix after administration of a single dose of 200 mg linzagolix (see “Dosage/Administration”). The unbound exposure to linzagolix was also unaffected by mild or moderate hepatic impairment. A 2- to 3-fold higher unbound mean exposure to linzagolix was reported in severe hepatic impairment (Child-Pugh class C) (see “Warnings and precautions” and “Contraindications”).

Patients with renal disorders

A clinical study conducted in patients with renal impairment (mild, moderate, severe or terminal renal failure), in which glomerular filtration rate (GFR) was assessed by creatine clearance, showed no relevant effect on total plasma exposure to linzagolix after administration of a single dose of 200 mg linzagolix. Conversely, C_{maxu}, $AUC_{u0\text{-}t}$ and $AUC_{u0\text{-}inf}$ for unbound linzagolix in plasma were increased by 30 %, 32 % and 33 %, respectively, in patients with mild renal impairment compared to healthy volunteers with normal renal function. A potential safety risk posed by long-term use can therefore not be ruled out (see “Dosage/Administration” and “Warnings and precautions”). In moderate or severe renal impairment, or terminal renal failure, mean exposure to unbound linzagolix was found to be approximately 1.5 times higher (in moderate renal impairment) or 2 times higher (in severe renal impairment and terminal renal failure) (see “Warnings and precautions”).

Preclinical data

Genotoxicity

A standard battery of *in vitro* and *in vivo* tests showed no evidence of a mutagenic or clinically relevant genotoxic potential for the drug.

Carcinogenicity

The carcinogenic properties of linzagolix were tested in a 26-week carcinogenicity study in Tg-RasH2 mice. There was no evidence of carcinogenicity induced by linzagolix up to the maximum dose of 500 mg/kg (corresponding to 13.2 times the maximum recommended human dose based on the AUC). In a 2-year carcinogenicity study conducted in rats, an increased incidence of endometroid adenocarcinomas in the uterus was observed in the intermediate (50 mg/kg) and high dose (500 mg/kg) groups (corresponding to 6.8 and 9.6 times the maximum recommended human dose based on the

AUC). A marginal increase in the incidence of mammary gland adenocarcinoma was observed only at the intermediate dose (50 mg/kg) (6.8 times the maximum recommended human dose based on the AUC). The clinical relevance of these results is unknown.
Non-carcinogenic histopathological findings in the ovaries and uterus (mouse) or in the ovaries and female mammary gland (rat) were considered to be related to the pharmacological effects of linzagolix.

Reproductive and developmental toxicity

Due to its mechanism of action, linzagolix prevented conception in fertility studies conducted in rats, reduced implantation and led to embryofoetal mortality, complete loss of the litter or termination of pregnancy in embryofoetal studies conducted in rats and rabbits.
No teratogenic effects and no adverse effects on pre- and postnatal development were observed in a study conducted in rats.
In the main embryonic development studies conducted in rats and rabbits, the NOAEL (No Observed Adverse Effect Level) for reproductive function and embryofoetal development was determined at 100 mg/kg and 3 mg/kg, respectively (corresponding to 5.9 and 0.004 times the maximum recommended human dose based on the AUC).

Lactation

Linzagolix has been shown to pass into the milk of rats. Up to 96 hours after administration, the concentration of radioactivity in milk was lower than in plasma (less than 0.3-fold).

Other information

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.

Special precautions for storage

Do not store above 30 °C.
Keep out of the reach of children.

Instructions for handling

Unused medicinal products or waste materials derived from them must be disposed of in accordance with the applicable regulations.

Marketing authorisation number

69692 (Swissmedic).

Packs

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

Pack containing 28 film-coated tablets (two blister packs with 14 film-coated tablets each). [B]

Pack containing 84 film-coated tablets (six blister packs with 14 film-coated tablets each). [B]

Not all pack sizes may be marketed.

Marketing authorisation holder

Future Health Pharma GmbH, 8620 Wetzikon

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