Summary of the Swiss Risk Management Plan (RMP)

Name of the medicinal product:	Yselty
Active substance(s):	Linzagolix
Version number of the current RMP:	1.1
Name of the marketing authorisation holder:	Future Health Pharma GmbH
Data lock point for the RMP:	05 November 2023

Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Yselty is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Yselty in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Future Health Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Yselty.

Part VI: Summary of the risk management plan

Summary of risk management plan for YSELTY (linzagolix)

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

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

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

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

I. The medicine and what it is used for

YSELTY is authorised in adult women of reproductive age for:

- treatment of moderate to severe symptoms of uterine fibroids,
- treatment of endometriosis-associated pain

(see SmPC for the full indication).

It contains linzagolix as the active substance and it is given orally.

Further information about the evaluation of YSELTY's benefits can be found in YSELTY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/yselty.

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

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

If important information that may affect the safe use of YSELTY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	• Bone mineral density decrease
Important potential risks	• Uterine endometrial and mammary gland adenocarcinoma • QT Interval Prolongation • Embryo-foetal toxicity • Liver Toxicity
Missing information	• Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT

II.B Summary of important risks

Important identified risk: Bone mineral density decrease	
Evidence for linking the risk to the medicine	Gonadotropin-Releasing Hormone (GnRH) antagonists such as linzagolix reduce serum oestradiol (E2) in a dose-dependent manner. These declines can result in dose-dependent bone mineral density (BMD) decrease due to increased bone resorption, which is most pronounced with high doses with which close to full E2 suppression is reached. The aim of lower doses and the use of hormonal ABT with higher doses is to achieve E2 levels within a range that limits BMD decrease. *Linzagolix 200 mg (without concomitant add-back therapy (ABT)):* Median levels of serum E2 for the 200 mg dose showed close to full suppression (<20 pg/mL), which was maintained at similar levels up to Week 24. BMD decrease related to linzagolix treatment was

	limited at 24 weeks. The protective effect of ABT was clearly observed with long term treatment (more than 6 months) at higher dose (200 mg). Individual categorical analysis shows that very few subjects experienced >8% BMD decrease, most of these subjects were in the 200 mg dose arm. BMD decrease after short term use of GnRH agonists generally shows partial to complete recovery within a few months after treatment completion. There was also evidence of recovery after short-term (6 months) full E2 suppression in the Phase 2 EDELWEISS linzagolix study in endometriosis which is in line with data from other GnRH agonists. *Linzagolix 200 mg (with concomitant ABT) and linzagolix 100 mg (with and without concomitant ABT):* Only moderate reductions of serum E2 were observed with the 100 mg dose, 100 mg+ABT and with 200 mg+ABT regimens (on-treatment medians ranging from 27.00 to 48.00 pg/mL) after 52 weeks of treatment. This results in BMD changes which were generally not clinically meaningful. Although overall the BMD changes in all groups were clinically not meaningful, the magnitude of BMD decrease was observed to be different for linzagolix 100 mg group, 100 mg+ABT and linzagolix 200 mg+ABT group (-2.36, -0.93 and -1.61 percent change from baseline at Week 52 at lumbar spine for the 100 mg, 100 mg+ABT and 200 mg+ABT dose, respectively). BMD decrease was more pronounced for linzagolix 100 mg group as compared to linzagolix 200 mg+ABT group and linzagolix 100 mg+ABT group (at week 24 and 52). This suggests that the changes in BMD with the 100 mg and 200 mg linzagolix dose were clearly seen to be mitigated by the concomitant use of hormonal ABT. When the 10-year fracture probability was assessed with the FRAX® tool (web version 4.2) in all PRIMROSE patients assuming continuing linear rates of BMD loss over up to 5 years of duration, the analysis suggests that the treatment could be given for at least 5 years without significant concerns about bone health. With regard to the 100mg dose, the mean FRAX probabilities remain well below intervention thresholds whereas the 200mg with concomitant ABT demonstrate even lower probabilities of future fracture risk (Study 20-OBE2109-006). Also, overall, there was evidence of recovery in BMD 24 weeks following treatment discontinuation at Week 52 in both groups.

	In the Phase 3 trials, bone mineral density loss at Month 6 was minimal at the 200 mg+ABT dose in endometriosis patients, lower than previously reported for UF patients, and similar to other oral GnRH receptor antagonists. Importantly, the rate of BMD change slowed or stabilized between Month 6 and Month 12, suggesting a non-linear pattern of BMD loss. There is no evidence of immediate fracture risk associated with linzagolix treatment.
Risk factors and risk groups	Major risk factors for decreased BMD include low body weight/ body mass index (BMI), chronic alcohol and/or tobacco use, family history of osteoporosis, hypogonadism, or chronic use of drugs that can reduce bone mass such as glucocorticoids and anticonvulsants. The use of linzagolix in these patients may further contribute to BMD decrease.
Risk minimisation measures	*Routine risk minimisation measures:* <u>Inclusion in the Summary of Product Characteristics (SmPC):</u> • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects <u>PL section:</u> • Section 2: What you need to know before you take YSELTY • Section 3: How to take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Uterine endometrial and mammary gland adenocarcinoma	
Evidence for linking the risk to the medicine	During a 104-week carcinogenicity study conducted in Wistar rats, higher incidence of uterine endometrial at high dose (500 mg/kg/day) and mammary gland adenocarcinoma at mid-dose (50 mg/kg/day) was observed; this higher incidence of uterine endometrial and mammary gland adenocarcinoma was judged to be incidental.

	The mechanism mediating this effect is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix. The data available are not sufficient to conclude on the potential clinical relevance of these findings. Therefore, only as a precaution "*Uterine endometrial and mammary gland adenocarcinoma*" is listed as important potential risk. During clinical studies, only 1 incidence of endometrial adenocarcinoma was observed in the PRIMROSE 1 and PRIMROSE 2 studies in the 100 mg+ABT group. For this event, a pre-existing lesion was detected in the screening biopsy. This event was considered as not related to linzagolix but to ABT treatment. In addition, 2 events of breast cancer (1 in the linzagolix 200 mg group, and the other in linzagolix 200 mg+ABT group (both from PRIMROSE 1 and 2 studies) were diagnosed. One more SAE of breast cancer was reported in Study KLH1201 in the 50 mg group. All three events were considered unrelated to linzagolix. Risks of ABT also include breast and endometrial cancer. The use of ABT is contraindicated in women with known, past or suspected breast cancer and oestrogen-dependent malignancy, and untreated endometrial hyperplasia. In the linzagolix program to date, there is no indication that these conditions, if present during treatment, are aggravated by linzagolix. In LGX 200 mg+ABT regimen in the Phase 3 endometriosis trials, no cancer SAEs were reported.
Risk factors and risk groups	No risk factors/groups have been identified.
Risk minimisation measures	*Routine risk minimisation measures:* <u>Inclusion in the Summary of Product Characteristics (SmPC):</u> • Section 5.3: Preclinical safety data *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: QT Interval Prolongation	
Evidence for linking the risk to the medicine	In Study 17-OBE2109-001 (TQTc study), a positive QTc prolongation signal was observed following single doses of both 700 mg and 200 mg linzagolix. The 700 mg and 200 mg doses, at 3 hours post dose, were found to prolong QTcF with least squares mean (LSM) of 9.92 msec (90% confidence interval (CI) 8.03 - 11.81) and 8.34 msec (90% CI 6.44 - 10.23), respectively. Post-hoc analyses accounting for heteroscedasticity produced similar results, with upper bounds of the 90% 2-sided CI of 11.55 and 9.91 msec for 700 mg and 200 mg linzagolix doses, respectively. With the exception of the above finding, the results of ECG readings performed in Phase 3 did not raise any safety concerns. There were no QTcF prolongations >500 ms in the Phase 2 or Phase 3 trials (except 1 Japanese subject in Phase 2 study KLH1204 who presented QT interval prolongation (QTc 519 ms) 29 days after the initial linzagolix dose of 50 mg). QT interval prolongation and TEAEs in the SOC *Cardiac disorders* were explored in accordance with ICH guidance *E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs (EMEA 2005).* The rates of the following TEAEs were compared in the treated and control subjects: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. Except for one event of syncope, none of the other PTs were reported to date in the linzagolix clinical development program; 1 subject in the 100 mg group reported 1 event of syncope which was not associated with QTcF prolongation (QTcF values ≤453 ms at all assessments). The results of ECG readings in the Phase 3 trials in subjects with endometriosis were in line with those observed previously in subjects with uterine fibroids and did not raise any safety concerns. There were no QTcF prolongations >500 ms in any of the Phase 3 trials, including extension trials, in subjects with endometriosis.
Risk factors and risk groups	Patients with known cardiovascular disease or family history of QT interval prolongation, hypokalaemia, or in patients consuming other concomitant medicinal products that prolong the QT interval, or in patients with coexisting disorders leading to increased linzagolix plasma levels.
Risk minimisation measures	*Routine risk minimisation measures:* Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.4: Special warnings and precautions for use.

	• Section 5.1: Pharmacodynamic properties • Section 5.2: Pharmacokinetic properties <u>PL section:</u> • Section 2: What you need to know before you take YSELTY *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Linzagolix reproductive and developmental toxicology was assessed in a female rat fertility study (0.16, 0.8, 4, 20, 100 mg/kg/day), an early embryonic development study in rats (100, 300, 1000 mg/kg/day), embryo-foetal development studies in rats (30, 100, 300 mg/kg/day) and rabbits (0.3, 3, 30 mg/kg/day), and pre- and postnatal developmental studies in rats (0, 30, 100, 300 mg/kg/day). Due to its mechanism of action, linzagolix prevented conception and reduced implantation in rats and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies. There were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring. In the clinical studies of linzagolix, patients were regularly evaluated for pregnancy, and any pregnancy that occurred was followed up for any evidence of treatment-related issues, including the pregnancy outcome and neonatal condition. In the Phase 3 trials in women with endometriosis, 4 pregnancies (0.7%) were reported. One of the 4 pregnancies occurred during the post-treatment follow-up period. With limited exposure of pregnant women to linzagolix, effects on human pregnancy are not known.
Risk factors and risk groups	A major risk factor for women of childbearing potential is non-use of contraception in the context of sexual activity during linzagolix treatment. Irregular bleeding may occur during treatment with linzagolix and may reduce the ability to recognize the occurrence of a pregnancy in a timely manner.

	Pregnancy testing should be performed if pregnancy is suspected, and linzagolix should be discontinued if pregnancy is confirmed.
Risk minimisation measures	*Routine risk minimisation measures:* Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.6: Fertility, pregnancy and lactation <u>PL section:</u> • Section 2: What you need to know before you take YSELTY *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Liver Toxicity	
Evidence for linking the risk to the medicine	Elevations in liver function tests (LFTs) are potentially a class effect with GnRH antagonists as it has also been reported with elagolix and relugolix treatment (Schlaff, 2020; Osuga, 2019, Carr, 2018 and MYFEMBREE® prescribing information). However, no reports of cases meeting Hy's law criteria/ of confirmed liver toxicity were reported to date in subjects treated with linzagolix. Supporting data from nonclinical studies in dogs and monkeys have shown that increases in serum liver enzymes could occur with linzagolix treatment. These studies concluded that linzagolix was not cytotoxic for hepatocytes and that increases in serum alanine transaminase (ALT) and glutamate dehydrogenase (GLDH) were likely to be attributable to induction of ALT and GLDH in the liver by the pharmacological effects of linzagolix. The findings were considered to be of low concern due to the therapeutic indices at the respective no-observed-adverse-effect levels (NOAELs), the absence of histological liver findings and the confirmation of reversibility following treatment free recovery periods. **Phase 3 trials (UF):**

	In linzagolix multiple dose studies, liver enzymes were closely monitored from Phase 1 to pivotal Phase 3 studies. Both Phase 3 uterine fibroid studies included regular testing of liver function parameters. Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and indirect bilirubin were assessed from blood samples taken at Screening, Day 1 and Weeks 4, 8, 12, 24, 28, 32, 36, 52, and during follow-up at the Week 64 visit. As observed with other GnRH antagonists, liver enzyme elevations occurred. The rate of elevations >3x ULN was low and none were associated with a bilirubin increase > 2 ULN and/or INR (International normalized ratio) increase > 1.5 ULN; i.e., no cases met criteria for Hy's law. In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies (N=1037) up to Week 24, 50 subjects (4.8%) reported 72 events of increases in liver function tests. The majority of these events were increases in GGT (28 subjects; 2.7%), ALT (22 subjects; 2.1%), or AST (15 subjects; 1.4%). Most were considered as related to linzagolix and very few led to permanent discontinuation of drug, but none were considered serious. Between Week 24 and Week 52 in the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies, increases in LFTs were reported infrequently as TEAEs (ALT increase in 0.7% (5/757), GGT increase in 0.5% (4/757), and AST increase in 0.4% (3/757)). Only few LFT abnormalities were reported as TEAEs at week 64 for both the studies.
Risk factors and risk groups	No risk factors/groups have been identified.
Risk minimisation measures	*Routine risk minimisation measures:* <u>Inclusion in the Summary of Product Characteristics (SmPC):</u> • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects <u>PL section:</u> • Section 2: What you need to know before you take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS

	See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	
Risk minimisation measures	*Routine risk minimisation measures:* Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures:* • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

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

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

YSELTY PASS Study

Purpose of the study:

To generate and evaluate data in patients taking YSELTY® in the real-world setting and for more than one year is needed to better understand certain safety parameters associated with long-term use. The overall study aim is to assess the long-term safety of YSELTY® when used in real life clinical practice.