イセルティ錠 100 mg
に関する資料

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キッセイ薬品工業株式会社

1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起源又は発見の経緯

KLH-2109（一般名称：リンザゴリクスコリン、以下本剤）は、キッセイ薬品工業株式会社が創製した経口投与可能な非ペプチド性の GnRH アンタゴニストである。本剤は GnRH 受容体拮抗作用によるゴナドトロピンの分泌抑制を介して、エストロゲン及びプロゲステロンの血中濃度を低下させることで、性ホルモン依存性疾患である子宮筋腫の症状を改善する効果が期待される。

子宮筋腫は、性ホルモン（エストロゲン及びプロゲステロン）に依存して初経から閉経の間に発症する婦人科腫瘍の中で最も発生頻度が高い良性腫瘍である [1)-3)]。一般的な症状は過多月経及びそれに伴う貧血、月経困難症、下腹部痛、圧迫症状、並びに不妊であり [2)-4)]、これらのうち最も多く認められる症状は過多月経である。過多月経は貧血を併発するほか、睡眠を妨げ疲労を増幅させる原因となる。また、子宮筋腫に伴う下腹部痛などの疼痛症状も多く認められ、これらの症状は日常生活や社会活動に支障を来し、全般的な生活の質（以下、QOL）を大きく損なう [5)]。また、月経随伴症状をはじめとする女性特有の健康課題は労働生産性の低下や経済損失にもつながり、本邦において月経随伴症状による労働生産性の損失が与える社会的な経済損失は年間約 6,000 億円と推計されている [6)]。月経随伴症状により年間で 11～14 日の欠勤、21～22 日の業務効率・パフォーマンスの低下を強いられており、月経随伴症状が労働生産性に与える影響は大きい。特に子宮筋腫患者では過多月経や疼痛症状などの重度の月経随伴症状があらわれるため労働生産性は著しく低下している [7)]。

子宮筋腫の治療は外科的治療法（手術療法及び低侵襲性療法）及び薬物療法に大別され、症状の有無及び挙児希望・子宮温存希望の有無等により治療方針が決定される。子宮筋腫の薬物療法には、対症療法及び内分泌療法がある。対症療法としては、過多月経に伴う鉄欠乏性貧血に対しては鉄剤、下腹部痛及びその他月経困難症に対しては非ステロイド性鎮痛薬及び漢方薬が用いられる [8),9)]。内分泌療法としては、主に GnRH アナログ（GnRH アゴニスト及び GnRH アンタゴニスト）が用いられており、過多月経や下腹痛等の諸症状の改善を目的として投与される。また、筋腫核の縮小効果を有しているため、手術時のリスクや侵襲性の軽減、閉経までの手術回避を目的とした投与が行われる [8)-10)]。GnRH アゴニストは、GnRH 受容体の刺激を介した受容体数の減少によりエストロゲン等の分泌を減少させることから、投与初期にエストロゲンの分泌が一過性に増加するフレアアップがみられ、それにより一時的に症状が悪化し、治療効果が発現するまでに時間を要する [8)]。さらに既存の GnRH アゴニストは、注射剤又は 1 日に複数回投与が必要な点鼻剤のみであり、患者の負担が大きい。一方 GnRH アンタゴニストは GnRH 受容体を直接阻害することで薬効を示すため、GnRH アゴニストにみられるような一時的な症状の悪化は認められず、速やかに治療効果が発現する。本邦では、経口 GnRH アンタゴニストであるレルゴリクスが使用されているが、食事の影響を受けるため食前の服用が規定されており [11),12)]、服薬アドヒアランスの低下が懸念される。また、P-gp の基質であることから P-gp 誘導剤や阻害剤との併用が注意喚起されている [11)]。以上より、子宮筋腫に対して様々な治療薬が用いられているものの、それぞれ課題があり、現在でも子宮筋腫に伴う症状による労働生産性の低下は社会的な課題となっていることから、1 日でも早く早期に症状を改善できる利

便性の高い新たな治療薬の開発が期待されている。

本邦では、少子高齢化による労働力不足や職場での男女間の賃金格差や管理職の割合などの不平等の課題を解消するため、2015 年に女性の職業生活における活躍の推進に関する法律（女性活躍推進法）が制定され [13]、女性の個性と能力が十分に発揮できる社会の実現に向け取り組んでいる。「女性活躍・男女共同参画の重点方針 2023（女性版骨太の方針 2023）」では、プライム市場上場企業を対象として、2030 年までに女性役員の比率として 30%以上を目指すことが掲げられており [14]、2024 年版では、2025 年までに 19%の中間目標が設定されるなど [15]、更なる女性の活躍が求められている。このような社会情勢において、身体活動の制限や精神的負担により日常生活や社会活動に支障を来し、労働生産性の低下や経済損失につながる月経随伴症状を速やか早期に改善できる薬剤の存在意義は大きい。

本剤は、非臨床試験で GnRH 受容体に対する高い親和性及び濃度依存的な拮抗作用を示し、用量依存的な E2 の分泌抑制作用を示した。さらに、性ホルモン依存性疾患である子宮内膜症モデルラットの子宮内膜切片移植部位の嚢胞体積を縮小させた。以上の結果より、本剤は既存の GnRH アナログと同様に性ホルモン依存性疾患である子宮筋腫や子宮内膜症等の症状を改善することに加えて、既存の GnRH アゴニストで指摘されているフレアアップによる一時的な症状の悪化を起こさず、速やかな E2 の分泌抑制により早期に症状を改善することが期待された。さらに、本剤は経口投与可能な薬剤であることから、剤形に起因する患者への負担を軽減する新たな薬剤となることが期待されたため、本剤の臨床試験を開始した。

1.5.2 開発の経緯

KLH-2109 の開発の経緯図を図 1.5.2-1～図 1.5.2-4 に示した。

本剤の臨床試験は 20[redacted] 年より開始し、日本人及び白人の健康女性を対象とした第 I 相臨床試験（KLH1101 試験）を実施した。本剤の開発は子宮内膜症に対する臨床試験が先行しており、20[redacted] 年より子宮内膜症患者を対象とした第 II 相試験（KLH1201、KLH1202、KLH1203 及び KLH1204 試験）を実施した。欧米ではこれらの日本のデータ（KLH1201～1203）に基づき 2017 年より子宮筋腫患者を対象とした第 III 相臨床試験（16-OBE2109-008 及び 16-OBE2109-009 試験）を実施し、2022 年に欧州にて子宮筋腫を適応症として承認を取得した。国内では 2022 年より子宮筋腫患者を対象とした第 III 相臨床試験（KLH2301 及び KLH2302 試験）を実施した。

試験項目 ＼ 年		[redacted]	添付資料番号
原薬	製造工程の開発の経緯		3.2.S.2
	規格及び試験方法		3.2.S.4
	安定性		3.2.S.7
製剤開発	製剤及び処方		3.2.P.1
	製剤開発の経緯 製造		3.2.P.2 3.2.P.3
	容器及び施栓系		3.2.P.7
添加剤の管理 製剤の管理			3.2.P.4 3.2.P.5
安定性			3.2.P.8

図 1.5.2-1　　開発の経緯図～品質に関する試験

試験項目 ＼ 年		添付資料番号
薬理	効力を裏付ける試験	4.2.1.1.1~9
	副次的薬理試験	4.2.1.2.1~2
	安全性薬理試験	4.2.1.3.1~6
薬物動態	分析法バリデーション	4.2.2.1.1~13
	吸収	4.2.2.2.1~4
	分布	4.2.2.3.1~10
	代謝	4.2.2.4.1~10
	排泄	4.2.2.5.1~3
	薬物相互作用	4.2.2.6.1~10
毒性	単回投与毒性試験	4.2.3.1.1~3
	反復投与毒性試験	4.2.3.2.1~10
	遺伝毒性試験/in vitro試験	4.2.3.3.1.1~2
	遺伝毒性試験/in vivo試験	4.2.3.3.2.1~2
	長期がん原性試験	4.2.3.4.1.1
	短期又は中期がん原性試験	4.2.3.4.2.1~2
	生殖発生毒性試験/Fertility[*1]	4.2.3.5.1.1~4
	生殖発生毒性試験/EFD[*2]	4.2.3.5.2.1~4
	生殖発生毒性試験/PPND[*3]	4.2.3.5.3.1~3
	生殖発生毒性/新生児	
	局所刺激性試験	
	その他の毒性試験/抗原性試験	
	その他の毒性試験/免疫毒性試験	
	その他の毒性試験/毒性発現の機序に関する試験	4.2.3.7.3.1~8
	その他の毒性試験/依存性試験	
	その他の毒性試験/代謝物の毒性試験	
	その他の毒性試験/不純物の毒性試験	4.2.3.7.6.1~6
	その他の毒性試験/その他の試験	4.2.3.7.7.1~2

*1 受胎能及び着床までの初期胚発生に関する試験
*2 胚・胎児発生に関する試験
*3 出生前及び出生後の発生並びに母体の機能に関する試験

図 1.5.2-2　　開発の経緯図～非臨床試験

年 試験項目	[redacted]	添付資料番号
生物学的同等性試験 (17-OBE2109-004)		5.3.1.2.1
第I相臨床試験 (KLH1101)		5.3.3.1.1
マスバランス試験 (KLH1103)		5.3.3.1.2
肝機能低下者試験 (18-OBE2109-009)		5.3.3.3.1
腎機能低下者試験 (18-OBE2109-010)		5.3.3.3.2
薬物相互作用（CYP3A4基質）及び食事の影響試験 (16-OBE2109-005)		5.3.3.4.1
薬物相互作用試験（OATP1B1/1B3阻害薬） (17-OBE2109-006)		5.3.3.4.2
薬物相互作用試験（CYP2C8基質） (18-OBE2109-006)		5.3.3.4.3
薬物相互作用試験（OAT3基質） (18-OBE2109-007)		5.3.3.4.4
薬物相互作用試験（OATP1B1基質） (22-OBE2109-001)		5.3.3.4.5
QT/QTc試験 (17-OBE2109-001)		5.3.4.1.1

図 1.5.2-3　　開発の経緯図～第 I 相臨床試験及び臨床薬理試験

年 試験項目	[redacted]	添付資料番号
国内第III相試験（1） （KLH2301）		5.3.5.1.1
国内第III相試験（2） （KLH2302）		5.3.5.1.2
海外第III相試験（PRIMROSE 1） （16-OBE2109-008）		5.3.5.1.3
海外第III相試験（PRIMROSE 2） （16-OBE2109-009）		5.3.5.1.4
国内子宮内膜症前期第II相試験（1） （KLH1201）		5.3.5.4.1
国内子宮内膜症前期第II相試験（2） （KLH1202）		5.3.5.4.2
国内子宮内膜症前期第II相試験（3） （KLH1203）		5.3.5.4.3
国内子宮内膜症後期第II相試験 （KLH1204）		5.3.5.4.4
海外子宮内膜症第II相試験（EDELWEISS） （15-OBE2109-001）		5.3.5.4.5

図 1.5.2-4　　開発の経緯図～第 II 相及び第 III 相臨床試験

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9) 百枝 幹雄．子宮筋腫・子宮内膜症・子宮腺筋症 診療マニュアル．初版．東京．株式会社診断と治療社；2013 Dec 20. p.18-27, 38-49

10) 産婦人科診療ガイドライン 婦人科外来編 2023．初版．東京．公益社団法人 日本産婦人科学会／公益社団法人日本産婦人科医会；2023 Aug 28. p.70-73

11) あすか製薬株式会社．レルミナ®錠 40 mg 添付文書．2023 年 2 月改訂（第 2 版）

12) あすか製薬株式会社．レルミナ®錠 医薬品インタビューフォーム．2023 年 3 月改訂（第 8 版）

13) 女性の職業生活における活躍の推進に関する法律（令和 2 年 6 月 1 日施行）

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1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況

主要国における本剤の承認状況を表 1.6.1-1 に示した。

本剤は、2022 年 6 月に「中等度から重度の子宮筋腫に基づく症状の治療」の効能・効果で EU 及びイギリスにおいて製造販売承認を取得した。さらに、2024 年 11 月に「子宮内膜症に対する薬物治療又は外科的治療歴を有する女性に対する子宮内膜症の対症療法」の効能・効果で EU において製造販売承認を取得した。2025 年 9 月現在、本剤は子宮筋腫及び子宮内膜症に対する治療薬として、30 ヵ国以上で承認されている。

なお、米国では 2021 年に ObsEva 社（米国における本剤の開発及び販売権を保有していた企業）が子宮筋腫の効能・効果で FDA へ承認申請を行ったものの、[redacted]により承認申請を取り下げた。

表 1.6.1-1　　主要国における承認状況（2025 年 9 月現在）

効能・効果	国名	許可年月日
子宮筋腫	EU	2022 年 6 月 14 日
	イギリス	2022 年 6 月 27 日
	オーストラリア	2024 年 9 月 5 日
子宮内膜症	EU	2024 年 11 月 22 日
	イギリス	2025 年 3 月 14 日

1.6.2 代表的な添付文書

1.6.2.1 EU の添付文書の概要

項目	内容
販売名	Yselty
一般的名称	Linzagolix（リンザゴリクス）
販売会社名	Theramex Ireland Limited
承認年月	2022 年 6 月
剤形・含量	Yselty 100 mg フィルムコート錠 ・リンザゴリクスコリン塩 100 mg を含有する。 ・ラクトース（賦形剤）119.4 mg を含有する。 ・直径 10 mm の円形、片面に「100」と刻印された淡黄色のフィルムコーティング錠。 Yselty 200 mg フィルムコート錠 ・リンザゴリクスコリン塩 200 mg を含有する。 ・ラクトース（賦形剤）238.8 mg を含有する。 ・19 mm×9 mm の楕円形、片面に「200」と刻印された淡黄色のフィルムコーティング錠。
効能・効果	生殖年齢の成人女性における以下の適応を有する。 ・中等度から重度の子宮筋腫に基づく症状の治療 ・子宮内膜症に対する薬物治療又は外科的治療歴を有する女性に対する子宮内膜症の対症療法
用法・用量	Yselty による治療は、子宮筋腫及び／又は子宮内膜症の診断及び治療の経験が豊富な医師によって開始・指導されるべきである。 投与方法 ・経口投与。 ・食事の有無に関わらず投与可能。 ・200 mg は、200 mg 錠を 1 回又は 100 mg 錠を 2 回投与する。 推奨用量 ・子宮筋腫 – Add-Back therapy（ABT）（エストラジオール 1 mg 及び酢酸ノルエチステロン 0.5 mg 錠を 1 日 1 回）を併用する場合は、100 mg 又は必要に応じて 200 mg を 1 日 1 回投与する。 – ABT が推奨されない又はホルモン療法を避けることが望ましい場合は、100 mg を 1 日 1 回投与する。 – 子宮及び子宮筋腫の体積縮小を目的とした短期間使用（6 ヵ月未満）の場合は、200 mg を 1 日 1 回投与する。治療を中止すると、子宮筋腫が大きくなることがある。長期使用による骨密度低下のリスクがあるため、ABT を併用しない 200 mg は 6 ヵ月を超えて投与するべきではない。 ・子宮内膜症 – ABT と併用し、200 mg を 1 日 1 回投与する。 ・治療の開始前に妊娠していないことを確認すること。 ・初回投与はなるべく月経周期の最初の週に行い、1 日 1 回継続して服用すべきである。 ・骨粗鬆症又は骨量減少のリスク因子を有する患者では、Yselty の投与開始前に Dual-energy X-ray Absorptiometry（DXA）スキャンを行うことが推奨される。 ・Yselty は休薬せずに投与可能である。治療開始から 1 年後に DXA スキャンを行うことが推奨され、その後も骨密度を継続してモニタリングすること。 ・飲み忘れた場合はできるだけ早く服用し、翌日からは通常とおりの時間に服用すること。
禁忌	・活性物質又は賦形剤に対する過敏症を有する患者 ・妊娠中又は授乳中の患者 ・骨粗鬆症の既往歴を有する患者 ・原因不明の性器出血を有する患者 ・ABT を併用する場合は、ABT に関する禁忌にも配慮する

警告及び使用上の注意	検診/問診 Yselty の投与開始又は再投与前に病歴（家族歴を含む）を聴取する。血圧を測定し、禁忌及び使用上の注意に従って検診を行う。治療中は標準的な診療方法に従って定期的な検診を行う。 Yseltyの投与開始前にホルモン性の避妊を中止する。Yseltyの投与開始又は再投与前に妊娠していないことを確認する。 骨密度 Yseltyの治療開始時に骨密度が正常であった患者の一部では、3～8%を超える骨密度の低下が報告された。 低外傷性骨折の既往歴、骨粗鬆症又は骨量減少のリスク因子（慢性的なアルコール及び／又はタバコの摂取、骨粗鬆症の強い家族歴、低体重など）を有する患者、骨密度に影響を及ぼす可能性のある薬剤（全身性コルチコステロイド、抗けいれん薬など）を服用している患者では、Yselty のベネフィットリスクを治療開始前に考慮すべきである。これらのリスクを有する患者では、Yselty による治療開始前に DXA スキャンを行うことが推奨される。 さらに、治療開始 1 年後には骨密度の低下が許容範囲内であることを確認するために、すべての患者で DXA スキャンを行うことが推奨される。その後は、Yselty の処方量に応じて、年 1 回（100 mg の場合）又は患者個々のリスクと過去の骨密度に基づいて担当医が決定した頻度（100 mg+ABT、200 mg+ABT の場合）で骨密度を測定することが推奨される。 骨密度低下のリスクが Yselty による治療の潜在的なベネフィットを上回る場合は、治療を中止すべきである。 肝機能低下者 重度の肝機能低下者（Child-Pugh C）へは可能な限り投与を避けること。軽度又は中等度の肝機能低下者（Child-Pugh A 又は B）での用量調節は不要。 腎機能低下者 中等度（eGFR=30～59 mL/min）、重度の腎機能低下者（eGFR<30 mL/min）又は終末期腎不全患者へは可能な限り投与を避けること。軽度の腎機能低下者（eGFR=60～89 mL/min）での用量調節は不要だが、有害事象をモニタリングすることが推奨される。 心血管障害／QT 延長 Linzagolix は QT 間隔をわずかに延長させるが、QT 延長や Torsade de Pointes の臨床的リスクを示すエビデンスはない。心血管疾患、QT 延長の家族歴又は低カリウム血症を有する患者及び QT 間隔を延長することが知られている医薬品との併用には注意すべきである。また、Linzagolix の血漿中濃度を上昇させる疾患を併発している患者でも注意すべきである。 避妊 ABT の併用有無に関わらず Linzagolix の避妊効果は証明されていない。妊孕性があり妊娠のリスクがある患者では、Yselty による治療中は効果的な非ホルモン性の避妊を行うこと。 月経出血パターンの変化及び妊娠を認識できなくなる可能性 Yselty による治療は通常、経血量を大幅に減少させてしばしば無月経を引き起こすため、妊娠を適時に認識できなくなる可能性があることを患者に知らせるべきである。妊娠が疑われる場合は妊娠検査を実施し、妊娠が確認された場合は治療を中止すべきである。 肝酵素 無症候性で一過性の肝酵素上昇が報告されている。黄疸など肝障害を反映する症状や徴候が現れた場合は、速やかに医師の診察を受けるよう患者に指導すべきである。黄疸が現れた場合は、治療を中止すべきである。急性肝機能検査異常の場合、肝機能検査値が正常に戻るまで Linzagolix の投与を中止しなければならないことがある。 肝機能パラメータに異常（正常値上限の 2 倍以上）のある患者は、Linzagolix の臨床試験から除外された。したがって、肝機能異常の既往を有する患者では、肝機能検査のベースラインを聴取し、定期的なモニタリングを実施すべきである。こ

	のような患者では注意して治療すべきである。 脂質レベル Linzagolix の投与により脂質レベルの上昇が観察された。これらは通常、臨床的に意義のない上昇であった。しかし、元より脂質レベルが高い患者では、脂質レベルをモニタリングすることが推奨される。 気分障害 Linzagolix を含む GnRH アンタゴニストによる治療において、うつ病、気分の変化、情緒不安定などの気分障害が認められている。うつ病及び／又は自殺念慮の既往歴を有する患者では注意が必要である。うつ病又はうつ病の既往歴を有する患者は、治療中に注意深くモニタリングすべきである。うつ病が深刻な程度まで再発した場合は、治療を中止すべきである。 CYP2C8 基質 治療域が狭く CYP2C8 の感受性が高い基質となる薬剤（たとえば、パクリタキセル、ソラフェニブ及びレパグリニド）を使用している患者では、可能な限り Yselty の投与を避けること。他の CYP2C8 基質と Yselty を併用する場合は、関連する有害事象の増加をモニタリングすることが推奨される。 ABT に関連する警告及び注意事項 ABT を併用する場合は、ABT に関連するすべての警告及び注意事項を考慮すべきである。 ラクトース ガラクトース不耐症、総ラクターゼ欠乏症、グルコース-ガラクトース吸収不良症といった稀な遺伝性疾患を有する患者に Yselty を投与すべきではない。 ナトリウム 本剤は、1 錠あたり 1 mmol（23 mg）未満のナトリウムを含有する。つまり実質的にナトリウムフリーである。
副作用	安全性プロファイルの概要 Yselty は 1605 例の患者を対象として、6 ヵ月又はそれ以上の主要な対照試験が行われた。これらの試験には、子宮筋腫患者及び子宮内膜症患者が含まれた。 子宮筋腫患者を対象とした主要な第 III 相臨床試験で報告された主な副作用は、ほてり及び頭痛であり、これらは高用量でより高頻度に認められ、ABT の併用により減少した。ほてりは、100 mg+ABT 群 5.2%、200 mg+ABT 群 9.6%、100 mg 群 10.1%及び 200 mg 群 31%で認められた。同様に、頭痛は高用量でより高頻度に認められ、ABT の併用により減少した（100 mg+ABT 群 1.4%、200 mg+ABT 群 2.4%、100 mg 群 4%及び 200 mg 群 6.2%）。 子宮内膜症患者において、200 mg+ABT 群で報告された主な副作用は、ほてり（6.3%）及び頭痛（5.7%）であった。 副作用の一覧表 Linzagolix に関連する副作用は、子宮筋腫患者を対象とした 2 つの主要な第 III 相臨床試験（Linzagolix 投与例 828 例及びプラセボ投与例 209 例）及び子宮内膜症患者を対象とした 2 つの主要な第 III 相臨床試験（Linzagolix 投与例 379 例及びプラセボ投与例 189 例）の 6 ヵ月までのデータに基づいて報告された。 頻度カテゴリと MedDRA の SOC で分類した副作用を以下の表に示した。各頻度カテゴリ内では、重症度の高い順に副作用を示した。頻度は、very common（≥1/10）、common （≥1/100 ～ <1/10）、uncommon （≥1/1000 ～ <1/100）、rare (≥1/10000～<1/1000)、very rare（<1/10000）及び unknown（利用可能なデータから推定不可）と定義した。

	Linzagolix 100 mg	Linzagolix 100 mg with ABT	Linzagolix 200 mg	Linzagolix 200 mg with ABT
精神障害				
Common	気分障害 [a]	気分障害 [a] リビドー減退	気分障害 [a] リビドー減退	気分障害 [a]
Uncommon	リビドー減退			リビドー減退
神経系障害				

Common	頭痛	頭痛	頭痛	頭痛
血管障害				
Very Common	ほてり		ほてり	
Common		ほてり		ほてり
Uncommon	高血圧	高血圧	高血圧	高血圧
胃腸障害				
Common		悪心／嘔吐 上腹部痛	悪心／嘔吐 便秘	悪心／嘔吐
Uncommon	上腹部痛		上腹部痛	便秘
肝胆道系障害				
Common	肝酵素増加	肝酵素増加	肝酵素増加	肝酵素増加
皮膚および皮下組織障害				
Common	多汗症		多汗症 寝汗	
Uncommon	寝汗			寝汗
筋骨格系および結合組織障害				
Common	関節痛	骨密度減少	関節痛 骨密度減少	
Uncommon	骨密度減少			関節痛 骨密度減少
生殖系および乳房障害				
Common	膣出血[b] 骨盤痛 月経出血パターンの変化[c]	膣出血[b] 骨盤痛	膣出血[b] 骨盤痛 外陰膣乾燥	膣出血[b] 骨盤痛 月経出血パターンの変化[c]
Uncommon	外陰膣乾燥	外陰膣乾燥 月経出血パターンの変化[c]	月経出血パターンの変化[c]	
一般・全身障害および投与部位の状態				
Common	無力症			
Uncommon			無力症	無力症

有害事象名は MedDRA バージョン 25.1 に従い翻訳
ABT：エストラジオール 1 mg 及び酢酸ノルエチステロン 0.5 mg 錠 1 日 1 回
a 気分動揺、感情不安定、情動障害、易刺激性、気分変化、不安、パニック発作、神経過敏、うつ病及び抑うつ気分を含む
b 膣出血、不正子宮出血、月経過多、過長過多不規則月経及び子宮出血を含む
c 月経遅延、不規則月経及び無月経を含む

過量投与	過量投与の報告はない。 過量投与した場合、患者の状態を注意深く観察し、対症療法及び支持療法で管理すべきである。 ABT を併用する患者では、エストロゲン及びプロゲスチンの過剰摂取により、ホルモンに関連した症状（悪心、嘔吐、乳房圧痛、腹痛、傾眠状態、疲労、消退出血が含まれるが、これらに限定されない症状）があらわれることがある。
薬物相互作用	CYP2C8 の基質となる薬剤 Linzagolix は、健康被験者においてレパグリニド（CYP2C8 の感受性の高い基質）の平均曝露量を 2 倍未満に増加させることが示されている。血漿中濃度が上昇する危険性があるため、主に CYP2C8 により代謝され治療域の狭いパクリタキセル、ソラフェニブ及びレパグリニドなどとの併用は可能な限り避けること。他の CYP2C8 基質と Yselty を併用する場合は、関連する有害事象の増加をモニタリングすることが推奨される。
特定の集団における使用	肝機能低下者 軽度又は中等度の肝機能低下者（Child-Pugh A 又は B）での用量調節は不要。重度の肝機能低下者（Child-Pugh C）へは可能な限り投与を避けること。 腎機能低下者 軽度の腎機能低下者（eGFR=60～89 mL/min）では、有害事象をモニタリングし、用量調節は不要。中等度（eGFR=30～59 mL/min）、重度の腎機能低下者（eGFR<30 mL/min）又は終末期腎不全患者へは可能な限り投与を避けること。 小児 中等度から重度の子宮筋腫に基づく症状の治療という適応で 18 歳未満の小児に Yselty が投与された経験はない。

1.6.2.2 EU の添付文書（原文）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg film-coated tablets

Yselty 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yselty 100 mg film-coated tablets

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

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

Yselty 200 mg film-coated tablets

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yselty 100 mg film-coated tablets

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

Yselty 200 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yselty is indicated in adult women of reproductive age for:
- treatment of moderate to severe symptoms of uterine fibroids,
- symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see section 5.1).

4.2 Posology and method of administration

Posology

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

The recommended dose of Yselty is:
For Uterine Fibroids:

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

For Endometriosis:

- 200mg once daily with concomitant hormonal add-back therapy

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

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

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

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

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

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

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

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

The safety and efficacy of Yselty in children aged under 18 years for the indication of treatment of endometriosis has not been established.

Method of administration

Oral use.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Medical examination/consultation

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

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

Bone mineral density

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

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

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

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

Hepatic impairment

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

Renal impairment

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

Cardiovascular disorders/QT prolongation

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

Contraception

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

Change in menstrual bleeding pattern and reduced ability to recognise pregnancy.

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

Liver enzymes

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

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

Lipid levels

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

Mood disorders

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

CYP2C8 substrates

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

Warnings and precautions relevant to ABT

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

Lactose

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

CYP2C8 substrate medicinal products

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

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

Breast-feeding

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Yselty was studied in 1605 patients in pivotal controlled trials for up to 6 months or more. These trials included uterine fibroid patients as well as endometriosis patients with short-term and long-term standing disease.

The safety data described in this section reflect the exposure to Yselty in four pivotal phase 3 trials. The most common adverse reactions reported in the pivotal phase 3 clinical studies in the uterine fibroid-treated population were hot flushes and headaches, which were reported with higher frequency at higher doses and less frequently when ABT was taken concomitantly (referred to as "with ABT"). Hot flushes were reported in 5.2%, 9.6%, 10.1% and 31% of women treated with 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively. Similarly, headaches were reported more frequently at higher doses and decreased with ABT (1.4%, 2.4%, 4% and 6.2% for 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively).

The most common adverse reactions reported in the endometriosis population treated with the recommended dose of 200 mg with ABT included hot flushes (6.3%) and headache (5.7%).

Tabulated list of adverse reactions

Adverse reactions associated with linzagolix are reported based on pooled data from two pivotal phase 3 studies in uterine fibroids (including 828 patients who received linzagolix and 209 patients who received placebo) and two pivotal phase 3 studies in endometriosis (including 379 patients who received linzagolix and 189 patients who received placebo) up to 6 months. These are tabulated in Table 1 below.

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

Table 1: Adverse drug reactions from pivotal clinical studies

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

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

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

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

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

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

Description of selected adverse reactions

Mood disorders
The most common mood disorder adverse reactions were reports of mood swings, which were reported in up to 2.5%of subjects in all linzagolix dose groups. Affect lability and anxiety were reported in 0.6% of subjects on linzagolix. Anxiety was only reported in the 200 mg groups with or without ABT. Reports of depression and depressed mood were infrequent. No more than 2 subjects in each of the linzagolix treatment groups reported depression or depressed mood in the phase 2 or phase 3 clinical studies. For specific recommendations, refer to section 4.4.

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

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

Endometriosis treated population:
After 6 months of treatment with the recommended dose linzagolix 200 mg with ABT, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were observed in 14% and 0% of patients, respectively. Following 12 months of treatment with linzagolix 200 mg with ABT, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were observed in 27% and 2% of patients, respectively (see Table 2).

Table 2: Proportion of patients with lumbar spine BMD change from baseline >3% and >8% at 6 months and at 12 months of treatment in PRIMROSE 1 and 2 and EDELWEISS 3 and 6

	PRIMROSE 1 and 2				**EDELWEISS 3 and 6**
	Linzagolix 100 mg	**Linzagolix 100 mg with ABT**	**Linzagolix 200 mg**	**Linzagolix 200mg with ABT**	**Linzagolix 200mg with ABT**
6 months of treatment					
Percentage of subjects (%) with BMD CfB > 3% / >8%	36 / 3	20 / 0	55 / 4	26 / 1	14 / 0
12 months of treatment					
Percentage of subjects (%) with BMD CfB > 3% / >8%	38 / 7	16 / 0	*	27 / 1	27 / 2

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

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

Vaginal haemorrhage
Vaginal haemorrhage (including reports of vaginal haemorrhage, uterine haemorrhage, metrorrhagia, menorrhagia, and menometrorrhagia) was reported during treatment with linzagolix. In the uterine fibroid studies, the most frequent adverse reactions were vaginal haemorrhage, metrorrhagia and menorrhagia which were reported in 13 (1.6%), 11 (1.3%) and 5 (0.6%) of subjects treated with linzagolix, respectively. Vaginal haemorrhage was reported more frequently in subjects in the 100 mg and 200 mg linzagolix with ABT group (up to 2.4%) compared to the groups without ABT (1%). Metrorrhagia was reported in 3 (1.5%), 3 (1.4%), 1 (0.5%) and 4 (1.9%) of subjects in the 100 mg, 100 mg with ABT, 200 mg, and 200 mg with ABT groups, respectively, and menorrhagia was reported for 1 (0.5%), 1 (0.5%), 2 (1.0%) and 1 (0.5%) of subjects in the linzagolix 100 mg, 100 mg with ABT, 200 mg and 200 mg with ABT groups, respectively.
In the endometriosis studies the safety profile confirmed the findings described above.

Reporting of suspected adverse reactions

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

4.9 Overdose

No case of overdose has been reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

Effects on pituitary and ovarian hormones
Administration of linzagolix results in dose-dependent suppression of luteinizing hormone and follicle-stimulating hormone, leading to decreased blood concentrations of estradiol and progesterone.

Uterine fibroid-treated population:
In the phase 3 studies, full suppression of serum estradiol (median < 20 pg/mL) was observed with linzagolix 200 mg from 4 to 24 weeks. Partial suppression was observed with linzagolix 100 mg, 100

mg with concomitant ABT (referred to as "with ABT") and 200 mg with ABT from 4 to 52 weeks, with median serum estradiol levels in the range of 20 to 60 pg/mL. Progesterone levels were maintained ≤ 3.1 ng/mL in 83% of women receiving linzagolix 200 mg for 24 weeks and 68% of women receiving linzagolix 100 mg for 52 weeks, and about 90% of women receiving linzagolix 100 mg with ABT or 200 mg with ABT for 52 weeks.

Endometriosis treated population:
Median serum estradiol levels for subjects receiving 200 mg with concomitant ABT were in the range of 20 to 60 pg/mL.

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

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

Clinical efficacy and safety

Uterine fibroid-treated population:

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

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

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

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

The primary efficacy endpoint was a response, defined as having an MBL of ≤ 80 mL and ≥ 50% reduction from baseline over the last 28 days before week 24. Treatment with Yselty with or without ABT resulted in a higher proportion of women with reduced MBL at week 24 compared to placebo. The percentage of responders was 56.4%, 66.4%, 71.4% and 75.5% with Yselty 100 mg, 100 mg with ABT, 200 mg and 200 mg with ABT, respectively in PRIMROSE 1 and 56.7%, 77.2%, 77.7% and 93.9% respectively in PRIMROSE 2 (Table 3). At week 52, the percentage of responders was 57.4%, 79.9% and 87.9% with Yselty 100 mg, 100 mg with ABT and 200 mg with ABT, respectively, in PRIMROSE 1 and 53.2%, 91.3% and 91.6%, respectively, in PRIMROSE 2.

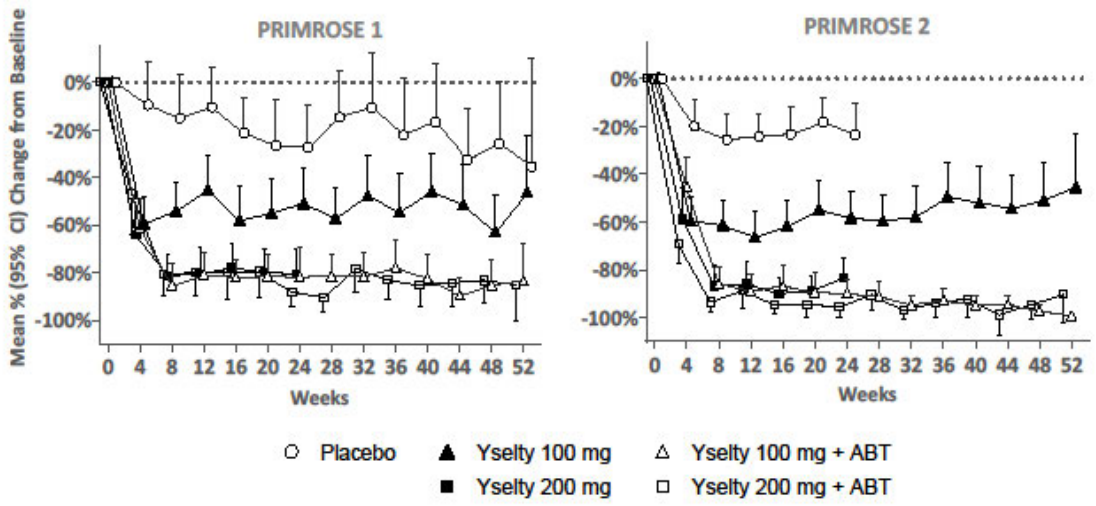
Table 3: Responders (women with reduced menstrual blood loss) at 24 weeks

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

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

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

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



In both pivotal phase 3 studies, improvements were observed in secondary endpoints after 24 weeks in the Yselty dose groups compared to placebo (Table 4), including an increased proportion of women achieving amenorrhea, reduced pain scores, higher haemoglobin levels in anaemic patients (< 12 g/dL at baseline) and increased health-related quality of life scores. These improvements were more

pronounced with Yselty 200 mg (with or without ABT) and Yselty 100 mg with ABT as compared to Yselty 100 mg.

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

Table 4: Secondary endpoints at 24 weeks

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

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

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

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

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

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

Bone mineral density

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

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

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

At 52 weeks, the mean percentage changes from baseline indicated a reduced rate of BMD loss: -2.36% with Yselty 100 mg, -0.93% with Yselty 100 mg with ABT and -1.61% with Yselty 200 mg with ABT. The level of treatment induced BMD loss in this population considered to be clinically meaningful is not well established, and will depend on the individual woman, but in general BMD losses of approximately 3% or more should be reviewed and monitored carefully. It is important to consider the individual woman's baseline BMD, age and overall osteoporosis risk profile when assessing an individual woman's BMD loss, and the benefit-risk of continuing treatment.

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

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

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

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

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

Endometriosis-treated population:

The efficacy of Yselty was evaluated in one phase 3, randomised, double-blind and placebo-controlled study, Edelweiss 3, including 484 women treated for up to 6 months. Amongst them, 356 women continued into the Edelweiss 6 extension study for an additional 6 months of treatment. A 6-month drug-free post-treatment follow-up evaluated the persistence of efficacy under long-term treatment.
This study was conducted primarily in Europe with about 10% of subjects being from US.

Eligible patients consisted in premenopausal women, aged 18 to 49 (inclusive) with surgical confirmed pelvic endometriosis and with moderate to severe endometriosis associated pain (EAP).

Women had a mean age of 34.9 years and mean body mass index was 24.27 kg/m2 (range 17.4 to 52.8). Approximately 98.6% of participating women were White.

The mean (SD) time since medical diagnosis of endometriosis was 5.20 (4.24) years. The most commonly reported symptoms, besides pelvic pain, were dyspareunia (88.0%), dyschezia (51.0%) and dysuria (26%). At baseline, 30% of patients presented adenomyosis and 18.2 % rectovaginal endometriosis nodes.

The majority of the study population of EDELWEISS 3 reported having undergone previous surgeries/procedures for endometriosis treatment before inclusion into the EDELWEISS studies. Previous medical treatments consisted of analgesics for pelvic pain, including opioids. The most frequently reported other pharmacotherapies for endometriosis treatment included dienogest, hormonal oral contraceptives and GnRH agonists.

Subjects were randomised to one of 3 treatments: placebo (N=162), Yselty 75 mg (N=160), Yselty 200 mg with concomitant ABT (estradiol 1 mg/ norethisterone acetate 0.5 mg, referred to as "with ABT") (N=162), all taken once daily. Subjects starting the extension study for additional 6 months stay on the same treatment regimen for 75mg and 200mg with ABT groups but subjects randomised to placebo were re-randomised 1/1 to Yselty 75 mg or Yselty 200 mg with ABT. Subsequently, all subjects underwent additional 6-month post-treatment drug-free period of follow-up to evaluate the persistence of efficacy under long-term treatment.

The two co-primary efficacy endpoints were clinically meaningful reduction of dysmenorrhea (DYS) and non menstrual pelvic pain (NMPP) over the last 28 days of randomized treatment up to the Month 3 visit along with a stable or decreased use of analgesics. These were defined as a reduction of 1.10 or greater from baseline pain for dysmenorrhea and a reduction of 0.80 or greater from baseline pain for non-menstrual pelvic pain, both measured on a 0 (no pain) to 3 (severe pain) verbal rating scale (VRS) using an electronic diary.

Treatment with Yselty 200 mg with ABT demonstrated statistically significant reductions in both co-primary endpoints of DYS and NMPP with a stable or decreased use of analgesics (see Table 6).

Table 6: Reduction of DYS and NMPP (VRS) at Months 3, 6 and 12 – responder analysis (Edelweiss 3, FAS and Edelweiss 6, TEAS)

Study	EDELWEISS 3				EDELWEISS 6
	Month 3		Month 6		Month 12
Treatment	Placebo	LGX 200 mg + ABT	Placebo	LGX 200 mg + ABT	LGX 200 mg + ABT
Nobs	159	156	115	122	111
Responders for DYS					
Percentage of responders	23.5	72.9	23.5	80.0	91.0
OR vs placebo	-	8.80	-	12.98	-
97.5% CI	-	4.86; 15.91	-	7.00; 24.06	-
Responders for NMPP*					
Percentage of responders	30.9	47.3	38.5	57.1	67.6
OR vs placebo	-	2.01	-	2.13	-
97.5% CI	-	1.18; 3.42	-	1.26; 3.60	-

ABT = add-back therapy; DYS = dysmenorrhea;; LGX = linzagolix; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale; Nobs = patients with observed data at this timepoint; OR = Odds Ratio; CI = Confidence Interval.
*Reduction of 1.1 (resp. 0.8) for DYS (resp. NMPP) in mean pelvic pain score within last 28 days prior to Month 3 or discontinuation, and stable or decreased use of analgesics for endometriosis within the same calendar days.

Statistically significant reductions were observed in the following secondary endpoints at 6 months in the LGX 200 mg+ABT group compared to placebo: DYS (VRS), NMPP (VRS), dyschezia (NRS), overall pelvic pain, OPP (NRS), and the ability to do daily activities measured using the pain dimension of EHP-30, see Table 7.

Table 7: Summary of analyses of secondary endpoints at Month 6

Endpoints	Placebo (N=162)	LGX 200 mg + ABT (N=162)	
	LSM (95% CI)	LSM (95% CI)	Diff with PBO (97.5% CI)
CfB in DYS (VRS)	-0.66 (-0.79; -0.53)	-1.83 (-1.96; -1.70)	-1.17 (-1.38; -0.97)
CfB in NMPP (VRS)	-0.66 (-0.77; -0.56)	-0.92 (-1.03; -0.82)	-0.26 (-0.43; -0.09)
CfB in dyschezia (NRS)	-1.41 (-1.71; -1.12)	-1.99 (-2.29; -1.70)	-0.58 (-1.05; -0.11)
CfB in OPP (NRS)	-2.19 (-2.55; -1.84)	-3.39 (-3.74; -3.03)	-1.19 (-1.77; -0.62)
CfB in EHP-30 pain dimension	-19.47 (-22.66; -16.28)	-35.60 (-38.73; -32.48)	-16.13 (-21.24; -11.02)

CfB = change from baseline; DYS = dysmenorrhoea; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; VRS = verbal rating; EHP-30 = Endometriosis Health Profile-30; LGX = linzagolix; LSM = least square mean
Scores were computed as mean of daily assessments on the last 28 days prior to Month 6 or discontinuation.

Persistence of efficacy was assessed in the linzagolix 200 mg with ABT group as these subjects continued on the same dosing regimen between Month 6 and Month 12.

Bone mineral density

BMD was assessed using DXA scan at baseline, during treatment (Months 6 and 12) and 6 months after the end of treatment. Subjects at significant risk of osteoporosis, with a history of, or known osteoporosis or other metabolic bone disease were excluded from these trials.

For the recommended dosing regimen linzagolix 200 mg with ABT, the mean percent change in lumbar spine BMD from baseline at Month 6 was - 0.79%. Of the subjects with available DXA readings at Baseline and at Month 12, the mean percent change corresponding to this period was -1.10% (Table 8).

Table 8: Mean percent change from baseline (CfB) in lumbar spine BMD at Month 6 and Month 12

	EDELWEISS 3 and 6	
	Placebo N = 162	**LGX 200 mg + ABT** N = 162
6 months of treatment		
Number of subjects	123	132
Mean percent CfB	0.77	-0.79
95% CI	0.40; 1.14	-1.15; -0.43
12 months of treatment		
Number of subjects	-	86
Mean percent CfB	-	-1.10
95% CI	-	-1.79; -0.41

LGX = linzagolix
CfB = change from baseline

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

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Biotransformation

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

Elimination

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

Special populations

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

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

Hepatic impairment
A clinical study conducted in female subjects with hepatic impairment (mild Child-Pugh A, moderate: Child-Pugh B and severe: Child-Pugh C) revealed no relevant effect on total plasma linzagolix exposure following administration of a single 200 mg dose of linzagolix. The unbound fraction of linzagolix was not affected by mild and moderate hepatic impairment; no dose adjustments with Yselty in patients with mild and moderate hepatic impairment are required (see section 4.2). Yselty

should not be used in women with severe hepatic impairment (Child-Pugh C) as 2- to 3-fold higher unbound linzagolix mean exposures were recorded (see section 4.4).

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

5.3 Preclinical safety data

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

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

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

Film-coating

Macrogol poly(vinyl alcohol) grafted copolymer (E1209)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Pack size of 28 film-coated tablets (two blisters of 14 film-coated tablets) or 84 film-coated tablets (six blisters of 14 film-coated tablets) per cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/001
EU/1/21/1606/002
EU/1/21/1606/003
EU/1/21/1606/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Theramex Poland Sp. z o. o.
Amsterdam Building,
ul. Poleczki 35,
02-822 Warszawa
Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard box for 100 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg film-coated tablets
linzagolix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/001 28 film-coated tablets
EU/1/21/1606/003 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yselty 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 100 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 100 mg tablets
linzagolix

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Theramex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard box for 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 200 mg film-coated tablets
linzagolix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
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Dublin 1
D01 YE64
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1606/002 28 film-coated tablets
EU/1/21/1606/004 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yselty 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Yselty 200 mg tablets
linzagolix

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Theramex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Yselty 100 mg film-coated tablets
linzagolix

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

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

What is in this leaflet

1. What Yselty is and what it is used for
2. What you need to know before you take Yselty
3. How to take Yselty
4. Possible side effects
5. How to store Yselty
6. Contents of the pack and other information

1. What Yselty is and what it is used for

Yselty contains the active substance linzagolix. It is used to treat
- moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are non-cancerous tumours of the uterus (womb).
- symptoms associated with endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (endometriosis is an often painful disorder in which tissue similar to the tissue that normally lines the inside of your uterus - the endometrium - grows outside your uterus).

Yselty is used in adult women (over 18 years of age) of childbearing age.

In some women, uterine fibroids may cause heavy menstrual bleeding (your ‘period’) and pelvic pain (pain below the belly button). Yselty is used for the treatment of your fibroids to stop or reduce bleeding and to decrease pain and pelvic discomfort associated with uterine fibroids.

Women with endometriosis can experience pelvic or lower abdominal pain, pain with menstrual periods and pain with intercourse. Yselty is used for the treatment of endometriosis to decrease the symptoms due to displaced tissue of the lining of the womb.

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

2. What you need to know before you take Yselty

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

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

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

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

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

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

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

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

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

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

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

Particularly inform your doctor or pharmacist if you are taking:
- repaglinide (a medicine used to treat diabetes)
- paclitaxel, sorafenib (medicines used to treat cancer)

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

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

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

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

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

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

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

3. How to take Yselty

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Uterine Fibroids:

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

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

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

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

Endometriosis:

- Two tablets of 100 mg Yselty taken once daily together with a medication containing the hormones oestrogen and progestogen (also known as add-back therapy). The add-back therapy is important to be taken with your Yselty tablets as this will help to reduce side effects including the risk and extent of bone mineral density loss.

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

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

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

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

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

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

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

4. Possible side effects

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

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

Common (may affect up to 1 in 10 people)
- mood disorders, such as mood swings, affect lability (i.e. rapid changes in emotions), anxiety, depression, irritability, emotional disorder
- excessive, irregular, or prolonged bleeding from the womb (uterine bleeding)
- vaginal dryness
- pelvic pain

- joint pain
- headache
- reduction in bone mineral density or bone strength
- increased liver enzyme blood levels
- nausea (feeling sick), vomiting, pain in stomach region
- constipation
- decreased interest in sex (libido)
- weakness
- increased sweating
- night sweats

Uncommon (may affect up to 1 in 100 people)
- high blood pressure

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

5. How to store Yselty

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

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

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

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

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

Yselty is provided in a cardboard box with 2 or 6 blisters containing 14 film-coated tablets (tablet) per blister.

Pack sizes: 28 or 84 film-coated tablets.

Not all pack sizes may be marketed.

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

Manufacturer
Theramex Poland Sp. z o. o.
Amsterdam Building,
ul. Poleczki 35,
02-822 Warszawa
Poland

This leaflet was last revised in

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

Package leaflet: Information for the patient

Yselty 200 mg film-coated tablets
linzagolix

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

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

What is in this leaflet

1. What Yselty is and what it is used for
2. What you need to know before you take Yselty
3. How to take Yselty
4. Possible side effects
5. How to store Yselty
6. Contents of the pack and other information

1. What Yselty is and what it is used for

Yselty contains the active substance linzagolix. It is used to treat
- moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are noncancerous tumours of the uterus (womb).
- symptoms associated with endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (endometriosis is an often painful disorder in which tissue similar to the tissue that normally lines the inside of your uterus - the endometrium - grows outside your uterus).

Yselty is used in adult women (over 18 years of age) of childbearing age.

In some women, uterine fibroids may cause heavy menstrual bleeding (your ‘period’) and pelvic pain (pain below the belly button). Yselty is used for the treatment of your fibroids to stop or reduce bleeding and to decrease pain and pelvic discomfort associated with uterine fibroids.

Women with endometriosis can experience pelvic or lower abdominal pain, pain with menstrual periods and pain with intercourse. Yselty is used for the treatment of endometriosis to decrease the symptoms due to displaced tissue of the lining of the womb.

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

2. What you need to know before you take Yselty

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

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

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

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

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

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

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

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

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

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

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

Particularly inform your doctor or pharmacist if you are taking:
- repaglinide (a medicine used to treat diabetes)
- paclitaxel, sorafenib (medicines used to treat cancer)

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

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

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

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

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

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

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

3. How to take Yselty

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

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

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

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

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

Endometriosis:
- One tablet of 200 mg Yselty taken once daily together with a medication containing the hormones oestrogen and progestogen (also known as add-back therapy). The add-back therapy is important to be taken with your Yselty tablet as this will help to reduce side effects including the risk and extent of bone mineral density loss.

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

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

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

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

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

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

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

4. Possible side effects

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

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

Common (may affect up to 1 in 10 people)
- mood disorders, such as mood swings, affect lability (i.e. rapid changes in emotions), anxiety, depression, irritability, emotional disorder
- excessive, irregular, or prolonged bleeding from the womb (uterine bleeding)

- vaginal dryness
- pelvic pain
- joint pain
- headache
- reduction in bone mineral density or bone strength
- increased liver enzyme blood levels
- nausea (feeling sick), vomiting, pain in stomach region
- constipation
- decreased interest in sex (libido)
- weakness
- increased sweating
- night sweats

Uncommon (may affect up to 1 in 100 people)
- high blood pressure

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

5. How to store Yselty

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

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

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

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

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

Yselty is provided in a cardboard box with 2 or 6 blisters containing 14 film-coated tablets (tablet) per blister.

Pack sizes: 28 or 84 film-coated tablets.

Not all pack sizes may be marketed.

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

Manufacturer
Theramex Poland Sp. z o. o.
Amsterdam Building,
ul. Poleczki 35,
02-822 Warszawa
Poland

This leaflet was last revised in

Other sources of information
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http://www.ema.europa.eu