Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Yselty 100 mg film-coated tablets
Yselty 200 mg film-coated tablets

linzagolix (as linzagolix choline)

PLGB 49876/0023-0024

Theramex Ireland Limited

LAY SUMMARY

Yselty 100 mg film-coated tablets
Yselty 200 mg film-coated tablets
linzagolix (as linzagolix choline)

This is a summary of the Public Assessment Report (PAR) for Yselty 100 mg and 200 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Yselty in this lay summary for ease of reading.

For practical information about using Yselty, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Yselty and what is it used for?
These products have been authorised by MHRA for Great Britain (GB, consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 14 June 2022 (EMEA/H/C/005442/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that these medicines are suitable for treating the specified indication.

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

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

How is Yselty used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (taken by mouth).

Treatment with Yselty will be prescribed by a doctor who is experienced in the care of patients with uterine fibroids.

The patient's doctor will work out the right dose of Yselty for their patient. The following dose options are possible:

- Either 100 mg Yselty (one tablet of 100 mg) or 200 mg Yselty (two tablets of 100 mg or one tablet of 200 mg), taken once daily together with another tablet once daily containing the hormones estradiol and norethisterone acetate (also known as add-back therapy). If the patient's doctor prescribes this add-back therapy, it is important to always take it with the patient's 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 or one tablet of 200 mg) 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).

The patient should:
- take the recommended dose **once daily**.
- start taking Yselty preferably in the first week of their menstrual cycle, which is the week they have bleeding.
- swallow the tablet(s) with one glass of water, with or without food.

Duration of use
The patient's doctor will work out how long to continue treatment, based on the risk of bone mineral density loss. The 200 mg dose (two tablets of 100 mg) without add-back therapy should be prescribed for no longer than 6 months.

The patient's doctor will check their bone mineral density by arranging a scan after the first 12 months of Yselty treatment to see if treatment can continue. If the patient continues Yselty treatment beyond one year, the patient's doctor will keep checking the patient's bone mineral density at regular intervals.

For further information on how Yselty is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take their medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Yselty have been shown in studies?
Yselty reduced bleeding associated with uterine fibroids in two main studies involving a total of 1,109 women. Women took either placebo (a dummy treatment) or one of two different doses of Yselty (100 mg or 200 mg once a day), with or without hormonal add-back therapy (ABT, which comprises estradiol 1 mg and norethisterone acetate 0.5 mg taken once daily).

After 24 weeks of treatment, more women taking Yselty with or without ABT reported monthly menstrual blood loss of fewer than 80 mL and at least 50% less blood loss than before the treatment, compared with placebo (56-76% of women using Yselty versus 35% of

women on placebo in the first study, 56-93% versus 29% in the second study). The highest number of patients who benefited from treatment in both studies was in the group of women treated with Yselty 200 mg plus ABT. The effect of Yselty was maintained until the end of the study (52 weeks).

What are the possible side effects of Yselty?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicines. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Why was Yselty approved?
Yselty was shown to improve bleeding associated with uterine fibroids when used with or without ABT. Yselty may impact bone density, and the product information includes recommendations on how to monitor patients for bone loss, and how to manage those with additional risk factors for developing osteoporosis. Aside from this, Yselty was generally well tolerated and its side effects are considered manageable.

The MHRA therefore decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

Yselty has been authorised with the condition to perform further studies to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Yselty?"

What measures are being taken to ensure the safe and effective use of Yselty?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Yselty. The RMP details the important risks of Yselty, how these risks can be minimised, any uncertainties about Yselty (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Yselty:

Summary of Safety Concerns	
Important identified risk	• Bone mineral density decrease
Important potential risk	• Uterine endometrial and mammary gland adenocarcinoma • QT Interval Prolongation • Embryo-foetal toxicity
Missing information	• Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Yselty are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Yselty product information, the Marketing Authorisation Holder (MAH) has committed to additional pharmacovigilance activities through the provision of effectiveness and safety data derived from a pharmacovigilance post-authorisation safety study to further evaluate the long-term effectiveness and safety of Yselty.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Yselty
Marketing Authorisations were granted in GB to ObsEva Ireland Limited (PLGB 43115/0001-0002) on 27 June 2022. Subsequent to Change of Ownership (COAs) procedures, the Marketing Authorisations were transferred on 04 October 2022 to the Marketing Authorisation Holder (MAH) Theramex Ireland Limited (PLGB 49876/0023-0024).

The full PAR for Yselty follows this summary.

This summary was last updated in November 2022.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Yselty 100 mg and 200 mg film-coated tablets (PLGB 49876/0023-0024, previously PLGB 43115/0001-0002) could be approved.

The products are approved for the following indication:

- the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The active substance, linzagolix (as linzagolix choline) 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.

These products have been authorised by MHRA for Great Britain (GB, consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 14 June 2022 (EMEA/H/C/005442/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (EMEA-002039-PIP01-16).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a full product specific waiver.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations were granted in GB to ObsEva Ireland Ltd. (PLGB 43115/0001-0002) on 27 June 2022. Subsequent to Change of Ownership (COAs) procedures, the Marketing Authorisations were transferred on 04 October 2022 to the Marketing Authorisation Holder (MAH) Theramex Ireland Limited (PLGB 49876/0023-0024).

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS
The MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

IV. NON-CLINICAL ASPECTS
The MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

V. CLINICAL ASPECTS
The MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations is recommended.

VI. RISK MANAGEMENT PLAN (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Bone mineral density decrease (Important identified risk)	*Routine risk minimisation measures*: • SmPC section 4.8 and PL section 4 • Contraindication for patients with known osteoporosis in SmPC Section 4.3 and PL section 2 • Recommendations in Sections 4.2 and 4.4 and PL section 2 to assess baseline BMD and to carefully weigh risk-benefit before commencing YSELTY treatment in patients with a history of a low-trauma or fragility fracture, or other risk factors for osteoporosis or BMD decrease. YSELTY should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment. • Recommendation to perform a DXA scan after 1 year of treatment for all women and thereafter annually (for YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (for YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT) in section 4.4. • Treatment duration limitation to 6 months for the 200 mg dose without concomitant ABT in SmPC section 4.2 and PL section 3. • Prescription-only medicine. *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activities*: • PRIMROSE 3 Study • YSELTY PASS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Uterine endometrial and mammary gland adenocarcinoma (Important potential risk)	*Routine risk minimisation measures*: • Prescription-only medicine. *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • Targeted follow-up questionnaires for uterine endometrial and mammary gland adenocarcinoma *Additional pharmacovigilance activities*: • YSELTY PASS
QT Interval Prolongation (Important potential risk)	*Routine risk minimisation measures*: • Warning in section 4.4 that linzagolix marginally increases the QT interval; recommendation to exercise caution when prescribing linzagolix in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products that prolong the QT interval; and caution when prescribing linzagolix in patients with co-existing disorders leading to increased linzagolix plasma level. • Prescription-only medicine. *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • Targeted follow-up questionnaire for QT interval prolongation *Additional pharmacovigilance activities*: • YSELTY PASS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryo-foetal toxicity (Important potential risk)	*Routine risk minimisation measures*: • Contraindication in pregnant women in SmPC Section 4.3 and 4.6 and in PL section 2 • Warning that linzagolix does not consistently inhibit ovulation and women on treatment may be at risk of pregnancy in the event of unprotected intercourse in SmPC section 4.6 and should be advised to use effective non-hormonal contraception to women of childbearing potential. • Warning on change in menstrual bleeding pattern and reduced ability to recognise pregnancy in SmPC section 4.4. • Prescription-only medicine. *Additional risk minimisation measures*: • None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • Targeted follow-up questionnaire for exposure in pregnancy/pregnancy outcome *Additional pharmacovigilance activities*: • YSELTY PASS
Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT (Missing Information)	*Routine risk minimisation measures*: • SmPC section 4.8 and PL section 4 • Contraindication for patients with known osteoporosis in SmPC Section 4.3 and PL section 2 • Recommendations in SmPC sections 4.2 and 4.4 and PL section 2 to assess baseline BMD and to carefully weigh risk-benefit before commencing YSELTY treatment in patients with a history of a low-trauma or fragility fracture, or other risk factors for osteoporosis or BMD decrease. • Recommendation to perform a DXA scan after 1 year of treatment for all women and thereafter annually (for YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: • None *Additional pharmacovigilance activities*: • YSELTY PASS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	and previous BMD assessment (for YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT) in section 4.4. • Prescription-only medicine. *Additional risk minimisation measures*: • None	

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

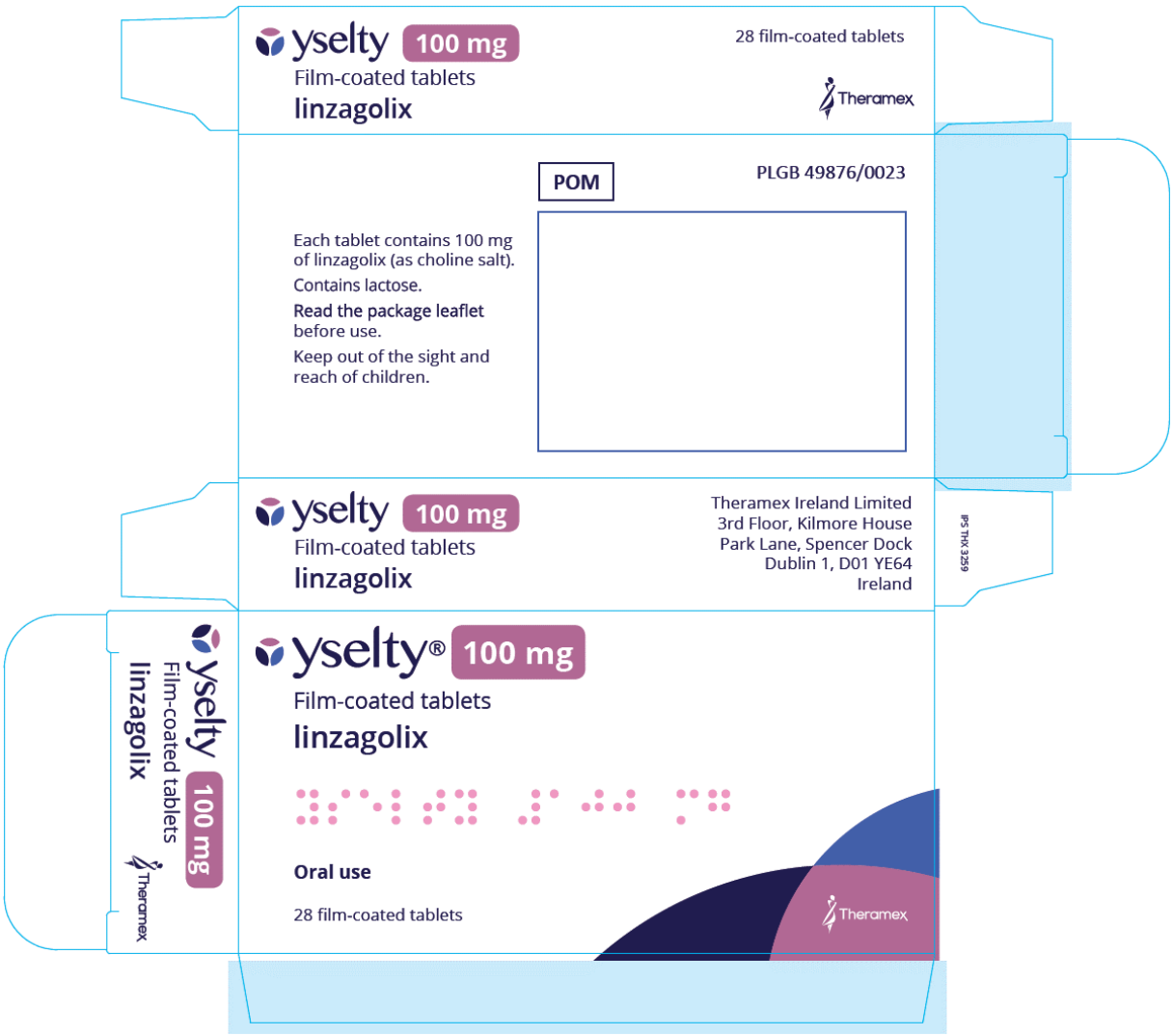
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The SmPCs, PIL and labelling are satisfactory.

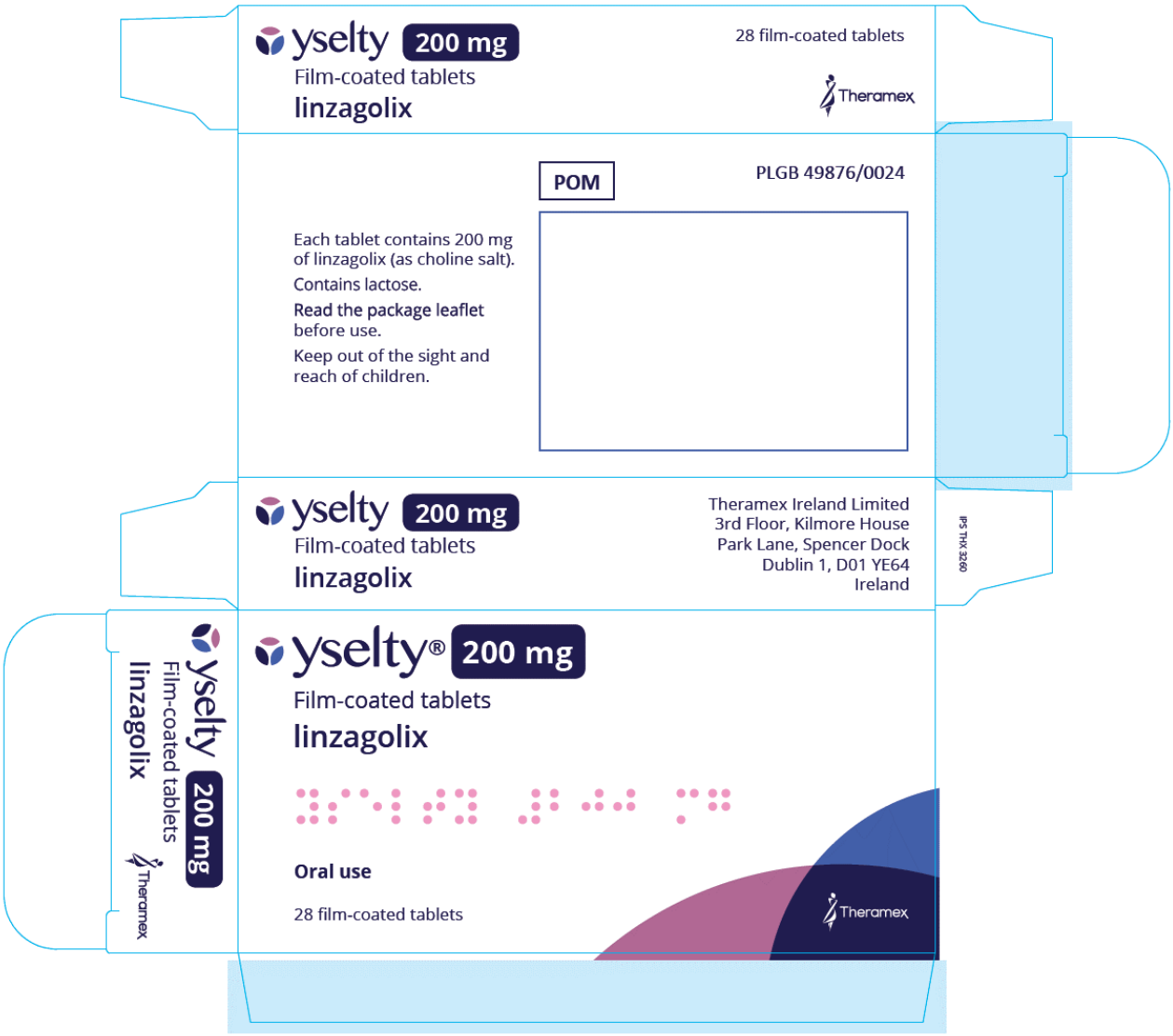
In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

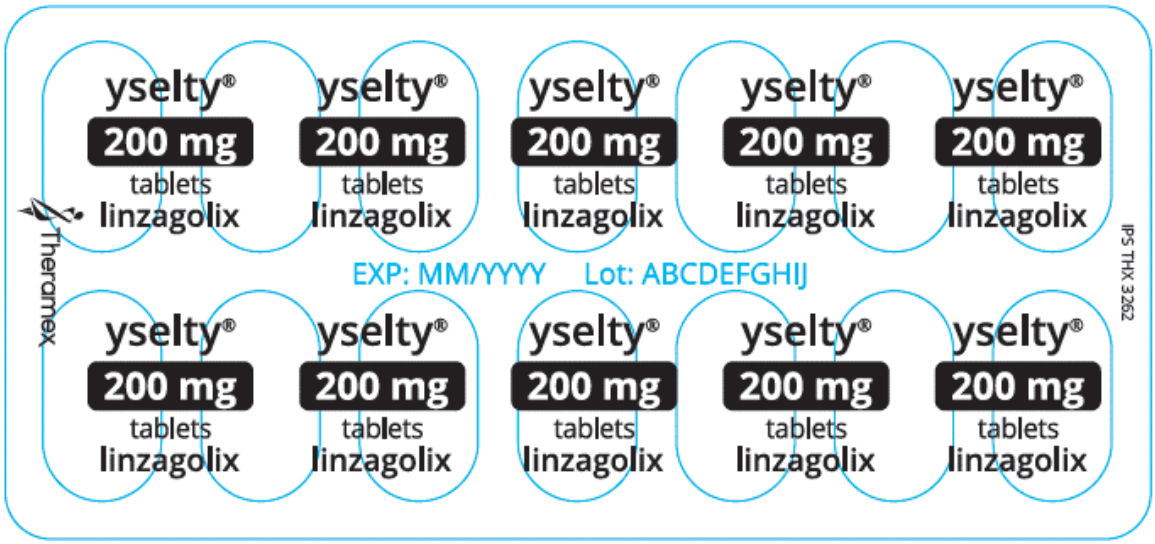
Representative copies of the labels for Yselty 100 mg and 200 mg film-coated tablets (PLGB 49876/0023-0024) at the time of GB licensing are provided below.

Yselty 100 mg film-coated tablets



Yselty 200 mg film-coated tablets


yselty 200 mg
Film-coated tablets
linzagolix
28 film-coated tablets
Theramex
POM
PLGB 49876/0024
Each tablet contains 200 mg of linzagolix (as choline salt).
Contains lactose.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Theramex Ireland Limited
3rd Floor, Kilmore House
Park Lane, Spencer Dock
Dublin 1, D01 YE64
Ireland
IPS THK 3269
yselty® 200 mg
Film-coated tablets
linzagolix
Oral use
28 film-coated tablets


yselty®
200 mg
tablets
linzagolix
EXP: MM/YYYY Lot: ABCDEFGHIJ
Theramex
IPS THX 3262

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the Marketing Authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

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