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

Inluriyo 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains imlunestrant tosylate equivalent to 200 mg imlunestrant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White, capsule shaped film-coated tablet of 14.0 x 7.5 mm, debossed with “LILLY” on one side and “1717” and an elongated 4-point starburst on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inluriyo is indicated as monotherapy for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen (for biomarker-based patient selection, see section 4.2).

In pre- or perimenopausal women, or men, Inluriyo should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Patient selection

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment based on the presence of an activating ESR1-mutation in tumour or in plasma specimens, using a CE-marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1-mutation should be assessed by an alternative validated test.

Posology

The recommended dose of imlunestrant is 400 mg orally (two 200 mg film-coated tablets), once daily.

It is recommended that treatment is continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Missed dose
If a dose is missed, it can be taken up to 6 hours after the time it is usually taken. After more than 6 hours, the dose should be skipped for that day. An additional dose should not be taken. On the next day, the dose should be taken at the usual time.

Vomiting
If the patient vomits after taking the dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Dose adjustments
If dose reduction is necessary, the dose should be decreased by 200 mg. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1 and 2. The treatment should be discontinued for patients unable to tolerate 200 mg once daily.

Table 1: Recommended dose modification for increased ALT and AST

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored during treatment, and as clinically indicated.

Toxicity[a]	Dose modification
Persistent or Recurrent Grade 2 AST or ALT, if baseline was normal	Suspend until toxicity resolves to baseline or Grade 1 if baseline was normal. Dose reduction is not required.
Grade 3 AST or ALT if baseline was normal **Or** Grade 2 or above AST or ALT if baseline was abnormal **Or** AST or ALT > 8 × ULN (whichever is the lower threshold)	Suspend until toxicity resolves to baseline or Grade 1 if baseline was normal. Resume at 200 mg dose level or discontinue if receiving 200 mg daily.
Grade 4 AST or ALT if baseline was normal	Discontinue dosing.
AST or ALT ≥ 3 × ULN concurrent with total bilirubin (TBL) ≥ 2 × ULN if baseline was normal in the absence of cholestasis **Or** AST or ALT ≥ 2 × baseline concurrent with TBL ≥ 2 × ULN if baseline was abnormal, in the absence of cholestasis	Discontinue dosing.

[a]NCI CTCAE v5.0
ULN: upper limit of normal

Table 2: Recommended dose modification for adverse reactions (except increased ALT and AST)

Toxicity[a]	Dose modifications
Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend until toxicity resolves to baseline or ≤ Grade 1. Dose reduction is not required.
Grade 3 (except non-hepatic asymptomatic laboratory changes)	Suspend until toxicity resolves to baseline or ≤ Grade 1. Resume at next lower dose level or discontinue if receiving 200 mg daily.

Grade 4 (except non-hepatic asymptomatic laboratory changes)	Suspend until toxicity resolves to baseline or ≤ Grade 1. Resume at next lower dose level or discontinue if receiving 200 mg daily. Closely monitor on resuming treatment.

[a] NCI CTCAE 5.0

Strong CYP3A inducers
Concomitant use of strong CYP3A inducers should be avoided. If strong CYP3A inducers cannot be avoided, the imlunestrant dose should be increased by 200 mg once daily (see section 4.5).

Strong CYP3A inhibitors
Concomitant use of strong CYP3A inhibitors should be avoided. If strong CYP3A inhibitors cannot be avoided, the imlunestrant dose should be decreased by 200 mg once daily (see section 4.5).

Special populations

Elderly
No dose adjustment is required on the basis of patient age (see section 5.2). Limited data are available in patients ≥ 75 years of age (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).
The dose should be reduced to 200 mg once daily in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. Limited data indicates that the exposure of imlunestrant may be increased in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 5.2). Treatment should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity.

Paediatric population

There is no relevant use of imlunestrant in the paediatric population in the indication of locally advanced breast cancer.

Method of administration

Inluriyo is for oral use.

Patients should take their dose at approximately the same time each day.

The tablets should be taken on an empty stomach at least 2 hours before or 1 hour after food (see section 5.2). The tablets should be swallowed whole (patients should not split, crush, or chew the tablets before swallowing). The effects of splitting, crushing, or chewing the tablets have not been investigated and may impact the safety, efficacy, or stability of the product. Exposure to the active substance could be harmful for caregivers.

4.3 Contraindications

Lactation (see section 4.6).

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Food effect

Imlunestrant exposures in the presence of a high-fat meal are unknown. The dose should be taken in the fasted state as higher exposures may occur with food.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Imlunestrant is metabolized by sulfation, CYP3A4 oxidation and direct glucuronidation.

Potential for other medicinal products to effect imlunestrant

Strong CYP3A inducers
Coadministration of imlunestrant with carbamazepine (a strong CYP3A inducer) decreased the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) of imlunestrant by 42 % and 29 %, respectively. Concomitant use of strong CYP3A inducers should be avoided. If strong CYP3A inducers cannot be avoided, the imlunestrant dose should be increased by 200 mg once daily (see section 4.2).

Strong CYP3A inhibitors
Coadministration of imlunestrant with itraconazole (a strong CYP3A inhibitor) increased the AUC and C_{max} of imlunestrant by 2.11-fold and 1.87-fold, respectively. Concomitant use of strong CYP3A inhibitors should be avoided. If strong CYP3A inhibitors cannot be avoided, the imlunestrant dose should be decreased by 200 mg once daily (see section 4.2).

Gastric acid reducing agents
Coadministration of imlunestrant with omeprazole (a proton pump inhibitor) had no clinically meaningful effect on the pharmacokinetics of imlunestrant.

Potential for imlunestrant to effect other medicinal products

CYP2D6 substrates
Imlunestrant increased the AUC and C_{max} of dextromethorphan (a CYP2D6 substrate) by 1.33-fold and 1.43-fold, respectively. Caution should be used when coadministering imlunestrant with CYP2D6 substrates for which a small increase in concentration leads to significant adverse events.

P-glycoprotein (P-gp) substrates
Imlunestrant increased the AUC and C_{max} of digoxin (a P-gp substrate) by 1.39-fold and 1.60-fold, respectively. Caution should be used when coadministering imlunestrant with P-gp substrates for which a small increase in concentration leads to significant adverse events.

BCRP substrates
Imlunestrant increased the AUC and C_{max} of rosuvastatin (a BCRP substrate) by 1.49-fold and 1.65-fold, respectively. Caution should be used when coadministering imlunestrant with BCRP substrates for which a small increase in concentration leads to significant adverse events.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of females of reproductive potential should be verified prior to starting treatment.

Females and males of reproductive potential should be advised to use highly effective contraception during treatment and for at least 1 week after the last dose (see section 5.3).

Pregnancy

There are no data from the use of imlunestrant in pregnant women. Based on the mechanism of action of imlunestrant and findings from embryofoetal toxicity studies in animals, imlunestrant can cause foetal harm when administered to pregnant women (see section 5.3). Imlunestrant should not be used during pregnancy and in women of childbearing potential not using contraception. If pregnancy occurs during treatment, the patient must be informed of the potential hazard to the foetus and potential risk of miscarriage.

Breast-feeding

It is unknown whether imlunestrant or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in the breast-fed infant, use during lactation is contraindicated (see section 4.3).

Fertility

Based on findings from animal studies (see section 5.3) and its mechanism of action, imlunestrant may impair fertility in females and males of reproductive potential.

4.7 Effects on ability to drive and use machines

Imlunestrant has no or negligible influence on the ability to drive and use machines. However, since fatigue and asthenia have been reported with imlunestrant, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common and clinically relevant adverse reactions were ALT increased (34.3 %), AST increased (33.2 %), fatigue (25.7 %), diarrhoea (22.5 %), nausea (20.1 %), and vomiting (9.0 %).

Adverse reactions leading to discontinuations of treatment in more than 1 patient included ALT increased (0.8 %) only.

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) displayed below are based on pooled data in 378 patients, treated with 400 mg imlunestrant once daily from a randomised, open-label, multicenter Phase 3 study (EMBER-3) and an open-label, multicenter, dose escalation and dose expansion phase 1a/1b study (EMBER).

In the following tables, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions in patients receiving imlunestrant

System organ class	Very common	Common
Metabolism and Nutrition Disorders		Decreased appetite [a]
Nervous System Disorders		Headache
Vascular Disorders		Venous thromboembolism [a] Hot flush [a]
Respiratory, Thoracic and Mediastinal Disorders		Cough [a]
Gastrointestinal Disorders	Diarrhoea Nausea	Vomiting Constipation Abdominal pain [a]
Musculoskeletal Disorders	Joint and muscular skeletal pain [b] Back pain	
General Disorders and Administration Site Conditions	Fatigue [a]	
Investigations [c]	ALT increased AST increased Triglycerides increased	

[a] Consolidated term consisting of analogous preferred terms.
[b] Consolidated term consisting of preferred terms: arthralgia, myalgia, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, pain in extremity, neck pain.
[c] Based on laboratory assessments.

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

Symptoms of overdose have not been established. The ADRs reported in association with doses higher than the recommended dose were consistent with the established safety profile (see section 4.8). The most frequent ADRs at higher doses were diarrhoea, nausea, fatigue and arthralgia. There is no known antidote for an overdose of imlunestrant. Patients should be closely monitored, and supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned, ATC code: Not yet assigned.

Mechanism of action

Imlunestrant is an antagonist and degrader of wild-type and mutant oestrogen receptor-α (ERα), leading to inhibition of oestrogen receptor-dependent gene transcription and cellular proliferation in ER-positive breast cancer cells.

Pharmacodynamic effects

Cardiac electrophysiology
The effect of imlunestrant monotherapy on the QTc interval was evaluated in 79 patients with matching pharmacokinetics and QTcF samples from EMBER. Results showed no effect of imlunestrant concentrations across the 200 mg to 1 200 mg dose range on QTc interval, with the upper bound of the 90 % CI of the mean delta QTc less than 10 ms at C_{max} of 400 mg (change from baseline of 1.72 ms; 90 % CI: -0.43, 3.87).

Clinical efficacy and safety

The efficacy and safety of imlunestrant was evaluated in EMBER 3, a Phase 3 global, randomized, open-label study for adult patients with ER-positive, HER2-negative, locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer (mBC), who have been treated with an aromatase inhibitor (AI), alone or in combination with a CDK4/6 inhibitor.

Eligible patients were pre-, peri- and postmenopausal women, or men, (≥ 18 years of age) with ER-positive, HER2-negative advanced breast cancer that had previously received an AI alone or combined with a CDK4/6 inhibitor in the adjuvant or metastatic setting. Patients had either: experienced recurrence while receiving or within 12 months of completing adjuvant treatment with an AI alone or with a CDK4/6 inhibitor for early breast cancer, experienced recurrence > 12 months after completing adjuvant treatment followed by disease progression on or after an AI alone or with a CDK4/6 inhibitor, or been diagnosed with *de novo* metastatic disease and had disease progression on or after an AI alone or with a CDK4/6 inhibitor. All patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and evaluable lesions per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, i.e., measurable disease or bone only disease with evaluable lesions. LHRH agonists were given to pre- and perimenopausal women, and men. Patients with presence of symptomatic metastatic visceral disease, and patients with cardiac comorbidity were excluded.

Patients were enrolled regardless of ESR1-mutation status. ESR1-mutational status was determined by blood circulating tumour deoxyribonucleic acid (ctDNA) using the Guardant360 CDx assay. A result was considered ESR1-positive if at least one of 34 predefined ESR1 variants was detected: E380A, E380D, E380K, E380Q, E380V, M421_V422delinsl, V422_E423del, V422del, S463F, S463P, L469V, L536F, L536G, L536H, L536I, L536K, L536N, L536P, L536Q, L536R, L536V, Y537C, Y537D, Y537G, Y537H, Y537N, Y537P, Y537Q, Y537S, D538E, D538G, D538H, D538N, D538V. Among these, 17 variants were identified within the EMBER-3 study population: E380K, E380Q, V422del, S463P, L469V, L536H, L536K, L536P, L536Q, L536R, Y537C, Y537D, Y537N, Y537S, D538E, D538G, D538N.

A total of 874 patients were randomised 1:1:1 between 3 treatment arms: 400 mg oral daily administration of Inluriyo (Arm A), investigators choice of standard of care (SOC) (fulvestrant or exemestane) (Arm B), or 400 mg oral daily administration of Inluriyo in combination with abemaciclib (Arm C). Among the 330 patients randomised to investigators choice endocrine therapy (Arm B), 292 received fulvestrant (90 %), and 32 received exemestane (10 %). Randomization was stratified by previous treatment with CDK4/6 inhibitor (yes vs. no), presence of visceral metastasis (yes vs. no), and region (East Asia vs. North America/Western Europe vs. Others). The demographics and baseline disease characteristics were well balanced between treatment arms. Baseline demographics of the overall study population were as follows: median age was 61 years (range: 27 - 89) and 13 % were ≥ 75 years, 99 % were female, 56 % were white, 30 % Asian, 3 % Black, and 11 % were other or missing. The majority of patients were treated in the second-line

advanced setting (67 %) versus the first-line setting (33 %), and the majority had received a prior CDK4/6i (60 %), 37 % received palbociclib, 15 % ribociclib and 3 % abemaciclib. Baseline ECOG performance was 0 (65 %) or 1 (35 %). Patient demographics for those with ESR1-mutated tumours were generally representative of the broader study population.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by investigator. Key secondary endpoint for EMBER-3 was overall survival (OS).

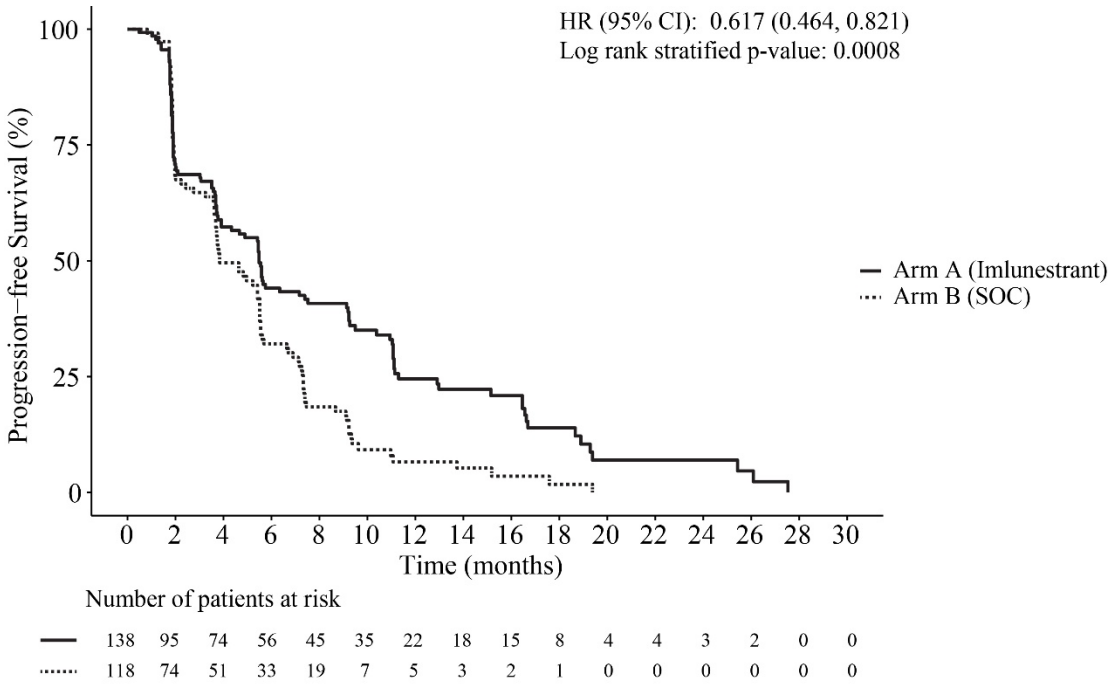
EMBER 3: Inluriyo monotherapy for patients with ESR1m
At the primary analysis (24 June 2024 cut-off), a statistically significant improvement in PFS was observed in patients who received Inluriyo monotherapy versus SOC in the ESR1m subpopulation. The comparison of Inluriyo monotherapy versus SOC was not statistically significant in the ITT population. Efficacy results in the ESR1m subpopulation are provided in Table 4 and Figure 1.

Table 4: Summary of efficacy data for patients with ESR1m treated with Inluriyo monotherapy in EMBER-3

	Inluriyo N = 138	**Standard of care N = 118**
Progression-free survival		
Number of events, n (%)	109 (79.0)	102 (86.4)
Median PFS, months (95 % CI) *	5.5 (3.9, 7.4)	3.8 (3.7, 5.5)
Hazard ratio (95 % CI) **	0.617 (0.464, 0.821)	
p-value (2-sided) **	0.0008	

CI=confidence interval; ESR1 = oestrogen receptor 1.
* Kaplan-Meier estimate; 95 % CI based on the Brookmeyer-Crowley method.
** From a Cox proportional hazards model and a stratified log-rank test stratified by previous treatment with CDK4/6 inhibitor (yes vs. no) and presence of visceral metastasis (yes vs. no).
Data cut-off date 24 June 2024

Figure 1: Kaplan-Meier Curve of progression free survival for patients with ESR1m treated with Inluriyo monotherapy in EMBER-3



In the CDK4/6i naïve subgroup, the median PFS in the Inluriyo arm was 11.1 months (95 % CI: 5.5, 16.5) compared to 5.7 months (95 % CI: 3.8, 7.4) in SOC arm (HR = 0.42; 95 % CI: 0.25, 0.72). In the CDK4/6i pre-treated subgroup, the median PFS in the Inluriyo arm was 3.9 months (95 % CI: 2.0, 6.0) compared to 3.7 months (95 % CI: 2.2, 4.6) in SOC arm (HR = 0.72; 95 % CI: 0.52, 1.0).

At the third OS interim analysis (18 August 2025 cut-off), 128 events were observed across the two arms, and the HR was 0.60 (95 % CI: 0.43, 0.86).

Paediatric population

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

5.2 Pharmacokinetic properties

In a population pharmacokinetic analysis, the steady-state mean (CV %) maximum concentration (C_{max}) of imlunestrant is 141 ng/mL (45 %) and the AUC_{0-24h} is 2 400 ng*h/mL (46 %) after administration of the recommended dose of 400 mg once daily. The C_{max} and AUC of imlunestrant increase proportionally over a dose range from 200 mg to 1 200 mg once daily (0.5 to 3 times the approved recommended dose).

Absorption

The mean (CV %) absolute bioavailability of imlunestrant after a single oral 400 mg dose is 10.5 % (32 %). The median time to reach peak plasma concentration (t_{max}) is approximately 4 hours.

Effect of food
Administration of imlunestrant 400 mg with a low-fat meal (approximately 400 - 500 calories with

100 - 125 calories from fat) increased C_{max} by 3.55-fold and $AUC_{(0-\infty)}$ by 2.04-fold compared to fasted administration. Imlunestrant exposures in the presence of a high-fat meal are unknown.

Distribution

In a population pharmacokinetic analysis, the mean (CV %) apparent central volume of distribution of imlunestrant is 4 310 L (69 %) in patients with advanced or metastatic breast cancer. Human protein binding of imlunestrant is 99.93 % to 99.96 % at clinically relevant concentrations.

Biotransformation

Imlunestrant is metabolized by sulfation, CYP3A4 oxidation and direct glucuronidation.

In vitro studies indicated that imlunestrant is a substrate of P-gp but not a substrate of BCRP, OCT1, OATP1B1, or OATP1B3.

Coadministration of imlunestrant with quinidine (P-gp inhibitor) had no clinically meaningful effect on the pharmacokinetics of imlunestrant.

Elimination

The elimination half-life of imlunestrant is approximately 30 hours and the mean (CV %) apparent clearance is 166 L/h (51 %). Following a single radiolabelled dose of imlunestrant 400 mg to healthy subjects, 97.3 % of the dose was recovered in feces and 0.278 % in urine.

Special populations

Effect of age, race, and body weight
In a population pharmacokinetic analysis, age (range: 28 years to 95 years), race and body weight (range: 36 kg to 145 kg) had no clinically meaningful effect on the pharmacokinetics of imlunestrant.

Hepatic impairment
There were no clinically relevant differences in the pharmacokinetics of imlunestrant in subjects with mild hepatic impairment (Child-Pugh A). The AUC of unbound imlunestrant increased 1.82-fold in subjects with moderate hepatic impairment (Child-Pugh B) and 2.33-fold in subjects with severe hepatic impairment (Child-Pugh C).

Renal impairment
In a population pharmacokinetic analysis, mild renal impairment (60 mL/min ≤ eGFR < 90 mL/min) and moderate renal impairment (30 mL/min ≤ eGFR < 60 mL/min) had no effect on the exposure of imlunestrant. The effect of severe renal impairment (15 mL/min ≤ eGFR < 30 mL/min) suggested exposure could be increased based on limited data in 2 trial participants. Pharmacokinetics of imlunestrant in patients on dialysis is unknown.

5.3 Preclinical safety data

Repeat-dose toxicity

Repeat-dose studies were conducted in rats and non-human primates to characterize toxicity. Adverse reactions observed at clinically relevant exposure levels were ovarian cysts and marked increases in ovarian weights, atrophy of the endometrium and myometrium of the uterus, epithelium and stroma of the cervix, and epithelium of the vagina in non-human primates. Minor, non-adverse vacuolation of macrophages in the mesenteric lymph node and ileum of non-human primates occurred at exposures that were 0.8-times and 11-times greater than human exposure (AUC_{0-24}) at 400 mg. Similar effects were observed in rats at exposures 4-times greater than human exposure (AUC_{0-24}) at 400 mg. Other important effects in rats were hyperplasia of the urinary bladder transitional epithelium, minimal to mild renal tubular degeneration, minimal inflammation of the renal pelvis, minimal to mild ocular lens

fibre degeneration, non-adverse hypertrophy of the pituitary pars distalis in females, non-adverse decrease in pituitary gland weights, and non-adverse atrophy or hypertrophy of the adrenal cortex, which occurred at exposures at least 4-times greater than human exposure (AUC_{0-24}) at 400 mg.

Genotoxicity

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity potential.

Reproductive and developmental toxicity

Based on findings in animals and its mechanism of action, imlunestrant may cause effects on male and female fertility which were generally reversible, and fetal harm when administered during pregnancy. Ovarian cysts and atrophy of the vagina, cervix, or uterus were observed in rats at and monkeys, at exposures that were 4-fold and 0.8-fold higher, respectively, than human exposure (AUC_{0-24}) at 400 mg. Additional reproductive findings occurred in rats and consisted of cessation of estrous cycling, lobular hyperplasia or hypertrophy of the female mammary gland epithelium, spermatid retention, and cellular debris in the lumen of the epididymis at exposures (AUC_{0-24}) at least 4-fold above that in humans. Administration of imlunestrant to pregnant rats during the period of organogenesis led to maternal toxicity, early delivery, embryo lethality, and teratogenic fetal effects at maternal exposures less than or equal to human therapeutic exposure.

Carcinogenicity

In the 26-week transgenic mouse carcinogenicity study, rasH2 mice were given oral doses of 5, 375, or 750 mg/kg imlunestrant, which caused an increased incidence of benign and malignant sex cord stromal tumours (granulosa and mixed cell) in the ovaries of mice at all dose levels. These doses correspond to 2-, 32-, and 41-times the human AUC at the recommended dose. Induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-oestrogen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium (E 468)
Hydroxypropylcellulose (E 463)
Magnesium stearate (E 470b)
Cellulose, microcrystalline (E 460)

Film-coating

Macrogols (E 1521)
Poly (vinyl alcohol) (E 1203)
Talc (E 553b)
Titanium dioxide (E 171)

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

Polychlorotrifluoroethylene (PCTFE) / Polyvinylchloride (PVC) blister sealed with aluminium foil in packs of 14, 28, 42, 56, 70 or 168 film-coated tablets.

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

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2003/001
EU/1/25/2003/002
EU/1/25/2003/003
EU/1/25/2003/004
EU/1/25/2003/005
EU/1/25/2003/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Recipharm Leganés S.L.U.
Calle Severo Ochoa 13
Leganés, Madrid 28914
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and 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 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

CARTONS FOR 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inluriyo 200 mg film-coated tablets
imlunestrant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg imlunestrant (as tosylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 film-coated tablets
28 film-coated tablets
42 film-coated tablets
56 film-coated tablets
70 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2003/001 14 film-coated tablets
EU/1/25/2003/002 28 film-coated tablets
EU/1/25/2003/003 42 film-coated tablets
EU/1/25/2003/004 56 film-coated tablets
EU/1/25/2003/005 70 film-coated tablets
EU/1/25/2003/006 168 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inluriyo 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

BLISTERS FOR 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Inluriyo 200 mg tablets
imlunestrant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Inluriyo 200 mg film-coated tablets
imlunestrant

▼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 using 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, pharmacist or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Inluriyo is and what it is used for

Inluriyo is a cancer medicine that contains the active substance imlunestrant and belongs to a group of medicines called selective oestrogen receptor degraders.

Inluriyo is used to treat adults with a certain type of breast cancer that is locally advanced or has spread to other parts of the body (metastatic) and whose cancer has not responded to or progressed further following at least one line of hormonal treatment. It is used when the cancer cells have oestrogen receptors (ER-positive) and do not have many receptors called human epidermal growth factor receptor 2 (HER2-negative). Inluriyo can only be used in patients who have certain changes (mutations) in a gene called ESR1.

In fertile woman and women in transition to menopause, and in men, treatment with Inluriyo should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

How Inluriyo works
Oestrogen receptors are proteins in cells that activate when the hormone oestrogen binds to them. By binding to these receptors, oestrogen can in some cases cause cancer cells to grow and multiply. Imlunestrant binds to oestrogen receptors in the cancer cells, which breaks them down and stops them from working. By blocking and destroying oestrogen receptors, imlunestrant can slow down the growth and spread of breast cancer and help to kill cancer cells.

2. What you need to know before you take Inluriyo

Do not take Inluriyo
- if you are breast-feeding.
- if you are allergic to imlunestrant or any of the other ingredients of this medicine (listed in section 6).

Children and adolescents
Inluriyo should not be used in children and adolescents under 18 years of age as it is not intended to treat breast cancer in this age group.

Other medicines and Inluriyo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way Inluriyo works and Inluriyo may affect the way other medicines work. For example, either medicine may become less effective or you may be more likely to experience side effects.

In particular, tell your doctor or pharmacist before taking Inluriyo if you are taking the following:
- **Dabigatran etexilate** (used to treat or prevent blood clots)
- **Dextromethorphan** (used to relieve cough)
- **Digoxin** (used to treat heart disease)
- **Rosuvastatin** (used to treat high cholesterol)
- **Itraconazole** (used to treat fungal infections)
- **Carbamazepine** (anti-epileptic used to treat seizures or fits)
- **Phenytoin** (anti-epileptic used to treat seizures or fits)
- **Rifampicin** (used to treat bacterial infections)
- **St. John's wort (**used to treat depression**)**

Pregnancy, breast-feeding and fertility
Pregnancy
Inluriyo may harm an unborn baby. If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are a man, or woman of childbearing age, you must use an effective method of contraception (birth control) during treatment with Inluriyo and for at least 1 week after stopping the treatment. Ask your doctor about suitable methods. If you are a woman who could become pregnant, your doctor will confirm that you are not pregnant before starting you on treatment with Inluriyo. This may include having a pregnancy test. Tell your doctor immediately if you become pregnant.

Breast-feeding
Do not breast-feed while taking Inluriyo. It is unknown whether Inluriyo passes into breast milk.

Fertility
Inluriyo may decrease fertility in men and women. Talk to your doctor or pharmacist for advice if you are planning to have a baby.

Driving and using machines
Inluriyo has no or negligible influence on your ability to drive and use machines. However, since fatigue and weakness have been reported in some patients taking Inluriyo, if you experience these side effects, you should be careful when driving or operating machinery.

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

3. How to take Inluriyo

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

The recommended dose of Inluriyo is 400 mg (two 200 mg film-coated tablets) taken once daily.

If you experience liver problems your doctor may lower your dose to 200 mg once daily.

If you get certain side effects while you are taking Inluriyo your doctor may lower your dose, pause your treatment until the side effects resolve, or stop treatment permanently.

Your doctor will tell you exactly how many tablets to take.

Take Inluriyo on an empty stomach; at least 2 hours before or 1 hour after food.

Inluriyo should be taken at about the same time every day. The tablets should be swallowed whole. Do not chew, crush, or split tablets before swallowing. This medicine could be harmful for people who are not taking Inluriyo.

If you take more Inluriyo than you should
If you have taken more Inluriyo than you should, contact a doctor or pharmacist immediately, or go to a hospital for advice. Take the tablets and this leaflet with you. Medical treatment may be necessary.

If you forget to take Inluriyo
- If less than 6 hours have passed since your usual time for taking a dose: Take the missed dose right away. Take the next dose at your usual scheduled time the next day.
- If more than 6 hours have passed since your usual time for taking a dose: Skip the missed dose. Take the next dose at your usual scheduled time the next day.
- If you experience vomiting: Do not take a double dose. Take the next dose at your usual scheduled time the next day.
- Do not take a double dose to make up for a forgotten tablet.

If you stop taking Inluriyo
Do not stop taking Inluriyo unless your doctor or pharmacist tells you to. Continuous treatment is important and stopping treatment without advice may worsen your condition.

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

4. Possible side effects

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

Tell your doctor, pharmacist or nurse if you notice any of the following:

Very common (may affect more than 1 in 10 people)
- Increased levels of liver enzymes, as measured in blood tests (alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased)
- Tiredness (fatigue)
- Joint, bone and muscle pain
- Diarrhea
- Increased levels of triglycerides, a type of fat in your blood
- Feeling sick (nausea)
- Back pain

Common (may affect up to 1 in 10 people)
- Constipation
- Abdominal (stomach) pain
- Cough
- Vomiting
- Headache
- Decreased appetite
- Hot flushes

- Blood clots in the veins (venous thromboembolism)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Inluriyo

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 carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

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 Inluriyo contains
The active substance is imlunestrant. Each film-coated tablet contains imlunestrant tosylate equivalent to 200 mg imlunestrant.

The other ingredients are:
- Tablet core: croscarmellose sodium (E 468), hydroxypropylcellulose (E 463), magnesium stearate (E 470b) and cellulose, microcrystalline (E 460) (see section 2 “Inluriyo contains sodium”).
- Film coating: macrogols (E 1521), poly (vinyl alcohol) (E 1203), talc (E 553b), titanium dioxide (E 171).

What Inluriyo looks like and contents of the pack
Inluriyo 200 mg is supplied as a white, capsule shaped film-coated tablet (tablet) of 14 x 7.5 mm, debossed with “LILLY” on one side and “1717” and an elongated 4-point starburst on the other side.

It is available in blister packs of 14, 28, 42, 56, 70 and 168 film-coated tablets.

Not all the pack sizes may be marketed.

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Other sources of information

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