swissmedic

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Swiss Public Assessment Report

Inluriyo, film-coated tablets

International non-proprietary name:	imlunestrant
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	Inluriyo 200 mg, film-coated tablets
Route(s) of administration:	oral
Marketing authorisation holder:	Eli Lilly (Suisse) SA
Marketing authorisation no.:	70233
Decision and decision date:	approved on 29 April 2026

Note:

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

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

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1 Terms, definitions, abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
BRCA	Breast cancer susceptibility gene
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinases 4 and 6CIConfidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	Estrogen receptor
ERA	Environmental risk assessment
ESR1	Estrogen receptor 1
ET	Endocrine therapy
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor 2
HPLC	High-performance liquid chromatography
HR	Hormone receptor
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LHRH	Luteinising hormone releasing hormone
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCF7	Michigan Cancer Foundation-7
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics

PFS	Progression-free survival
P-gp	P-glycoprotein
PGR	Progesterone receptor
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SERD	Selective estrogen receptor degrader
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak drug concentration
TNBC	Triple-negative breast cancer
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UGT	Uridine diphosphate glucuronosyltransferase
WT	Wild-type

2 Background information on the procedure

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

New active substance status
The applicant requested new active substance status for imlunestrant in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Inluriyo is indicated for the treatment of adult patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 (ESR1)-mutated, advanced or metastatic breast cancer, following prior endocrine therapy.

2.2.2 Approved indication

Inluriyo is indicated as monotherapy for the treatment of adult female patients with ER-positive, HER2-negative, ESR1-mutated, advanced or metastatic breast cancer, who have disease progression following prior treatment with an endocrine based regimen.

In pre- or perimenopausal women, Inluriyo should be combined with an LHRH agonist.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose of imlunestrant as monotherapy is 400 mg (two tablets of 200 mg) orally once daily.
Pre- or perimenopausal women and men should receive an LHRH agonist in accordance with current clinical treatment standards when undergoing treatment with Inluriyo.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	21 February 2025
Formal control completed	4 March 2025
List of Questions (LoQ)	1 July 2025
Response to LoQ	8 September 2025
Preliminary decision	9 December 2025
Response to preliminary decision	1 March 2026
Final decision	29 April 2026
Decision	approval

3 Medical context

Breast cancer (BC) is the most commonly diagnosed cancer among women in Switzerland, with an incidence of 77.4 for every 100,000 women (Global Cancer Observatory: Cancer Today (version 1.1), accessed 26 May 2026). Male BC is rare, representing approximately 1% of cancers that occur in men and approximately 1% of all BCs worldwide (Gucalp A, Traina T, Eisner J et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat. 2019 Jan;173(1):37-48. doi: 10.1007/s10549-018-4921-9).

BC is categorised into 3 major subtypes based on the presence or absence of molecular markers for hormone receptors (HR), i.e. ER and progesterone receptors (PGR), and HER2: HR-positive/ HER2-negative BC, HER2-positive BC, and triple-negative BC (TNBC), which lacks all 3 standard molecular markers. The HR, HER2-negative subtype accounts for approximately 70% of all breast cancer cases. Around 90% of HR positive breast cancer are ER positive.
In patients whose disease progresses during or after endocrine therapy (ET), with or without a cyclin-dependent kinases 4/6 (CDK4/6) inhibitor (used either as adjuvant treatment or as first-line therapy in the metastatic setting), second-line treatment options include: the selective estrogen receptor degrader (SERD) fulvestrant plus a CDK4/6 inhibitor for women not previously exposed to a CDK4/6 inhibitor, subsequent lines of ET depending on prior treatments, everolimus in combination with exemestane, targeted therapies in the presence of specific mutations such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) or breast cancer susceptibility gene (BRCA), or chemotherapy in the case of visceral crisis. Premenopausal women must receive ovarian function suppression in addition to all endocrine-based therapies. In addition, elacestrant, an oral SERD, is indicated for use in postmenopausal patients with ESR1 mutations following treatment with aromatase inhibitors (AI) or fulvestrant and CDK4/6 inhibitors.

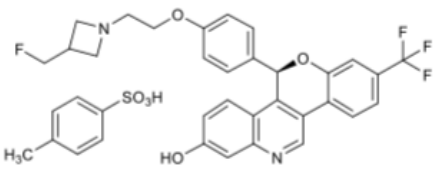
A substantial proportion of patients with ER-positive breast cancer develops endocrine resistance with genomic and epigenetic alterations of ESR1, encoding for the ER, being one of the causes. Mutations of the ESR1 gene have a high prevalence (6-55%) in patients with metastatic BC who have previously received ET. Many BCs that are resistant to AI or tamoxifen still depend on ER signalling and show a partial sensitivity to treatment with SERDs. At present, fulvestrant and elacestrant are the only SERDs available in this setting. However, PFS rates were also lower among patients with ESR1 mutant cancers when treated with fulvestrant as compared to patients with wild-type (WT) tumours, and elacestrant is approved solely for postmenopausal patients after a CDK 4/6 inhibitor. Effective treatment options are needed for these patients.

4 Quality aspects

4.1 Drug substance

INN: Imlunestrant (as tosylate salt)
Chemical name:
5H-[1]Benzopyrano[4,3-c]quinolin-2-ol, 5-[4-[2-[3-(fuoromethyl)-1-azetidinyl]ethoxy]phenyl]-8-(trifluoromethyl)-,(5R)-,4-methylbenzenesulfonate (1:1)

Molecular formula parent compound: $C_{29}H_{24}F_4N_2O_3$
Molecular formula tosylate salt: $C_{29}H_{24}F_4N_2O_3.C_7H_8O_3S$
Molecular mass parent compound: 524.52g/mol
Molecular mass tosylate salt: 696.71g/mol
Molecular structure:



Physicochemical properties: White to practically white to yellow powder with defined physicochemical properties, stereochemistry and crystal form.

The synthetic process leads to the desired form.

Specifications include the relevant test parameters as recommended by the relevant international Council for Harmonisation (ICH) guidelines and are compliant with the current European pharmacopoeia (Ph.Eur.). The analytical methods are adequately described and the methods are validated.

Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition:
White immediate release tablet containing 200mg imlunestrant with modified capsule shape, one side debossed with an elongated 4-point starburst over “1717” and the other side debossed with “LILLY”.

The manufacturing process consists of standard unit operations and yields appropriate quality.

Specifications include the relevant test parameters as recommended by relevant ICH guidelines and are compliant with the current Ph.Eur. The analytical methods are adequately described and the methods are validated.

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

4.3 Quality conclusions

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

5 Nonclinical aspects

5.1 Pharmacology

Imlunestrant demonstrated high-affinity binding to both WT and mutant estrogen receptor α (ERα or ESR1), with inhibitory constant values of 0.63 nM and 2.8 nM, respectively, and effectively degraded both forms (half maximal inhibitory concentration (IC_{50}) values approximately 3 nM). Suppression of ERα activity was evidenced by reduced transcription of ER-regulated genes, including the progesterone receptor (PGR). No imlunestrant-related PGR induction was observed in estradiol-stimulated Michigan Cancer Foundation-7 (MCF7) ER-positive breast cancer cells (IC_{50} > 2 µM), confirming that imlunestrant functions as a pure ERα antagonist.
In vitro, imlunestrant potently inhibited proliferation of ESR1 WT MCF7 cells, ESR1-Y537N MCF7 mutant cells, and ST941/C ESR1-Y537S mutant breast cancer patient-derived xenograft cell lines (IC_{50} values 3.49 nM, 16.7 nM, and 6.8 nM, respectively). Across a panel of breast cancer cell lines, 11 out of 12 ER+ cell lines were sensitive to imlunestrant (IC_{50} < 100 nM), whereas all ER-negative cell lines were insensitive (IC_{50} > 2 µM).
In vitro combination studies with the CDK4/6 inhibitor abemaciclib revealed synergistic or additive effects on cell proliferation inhibition in 4 out of 5 ER-positive breast cancer cell lines.
The two primary metabolites of imlunestrant (M1 and M2) exhibited significantly lower pharmacological activity – 35- to 136-fold less potent – compared to imlunestrant in ERα degradation, PGR inhibition, and cell proliferation assays.
In murine xenograft models harbouring WT and mutant ESR1 cell-derived tumours, as well as in patient-derived xenograft models, daily oral administration of imlunestrant resulted in sustained and significant tumour growth reduction. Imlunestrant demonstrated superior efficacy compared to fulvestrant in these models. Additionally, imlunestrant penetrated the blood-brain barrier, inhibited the growth of MCF7-fLuc breast cancer cells implanted in the brain, and improved overall survival (OS).
Imlunestrant exhibited high selectivity as an ERα antagonist, with no significant activity against other nuclear hormone receptors. A comprehensive screen of kinases and human G-protein-coupled receptors revealed no off-target pharmacology. Furthermore, imlunestrant displayed no uterotrophic effects in immature female rats.
In terms of safety pharmacology, imlunestrant showed no effects on the human ether-à-go-go-related gene cardiac potassium channel or the human cardiac sodium channel Nav 1.5. No dedicated *in vivo* safety pharmacology studies were conducted, but endpoints were assessed in repeat-dose toxicology studies in monkeys. Imlunestrant did not affect cardiovascular, respiratory, or central nervous system functions.

5.2 Pharmacokinetics

The pharmacokinetics of imlunestrant were characterised in mice, rats, and monkeys. Following oral administration, imlunestrant was slowly absorbed, with a time to peak drug concentration (T_{max}) of approximately 4 hours in rats and 8.3 hours in monkeys (T_{max} in humans was 4.37 hours). The clearance of imlunestrant was low to moderate, and its half-life ($T_{1/2}$) was 22.2 hours in mice, 20.7 hours in male rats, 15.2 hours in female rats, and 12.2 hours in monkeys, compared to 30.1 hours in humans. After repeated daily oral administration in rats and monkeys, systemic exposure increased approximately proportionally to dose in rats, while the increase was less proportional in monkeys. No sex-related differences in systemic exposure were observed. There was no significant accumulation of imlunestrant or its metabolites (assessed in rats only). The oral bioavailability of imlunestrant ranged from 8% to 44% in animals and was 10.5% in humans.
In vitro plasma protein binding of imlunestrant was similarly high across species, including mice, rats, dogs, monkeys (99.83% to 99.90%), and humans (99.89%). Quantitative tissue distribution studies in albino and pigmented rats demonstrated rapid and widespread distribution into tissues following oral administration of [^{14}C]-imlunestrant. T_{max} in most tissues was ≤8 hours, with the exception of the eye/uveal tract, harderian gland, epididymis, preputial gland, and testis. Radioactivity persisted in the uveal tract up to 672 hours post-dose, suggesting binding to melanin. [^{14}C]-imlunestrant-derived

radioactivity was also detected in the brain and spinal cord, although levels had dropped below the quantitation limit by 48 hours post-dose.
Glucuronidation and sulfation were the predominant biotransformation pathways in animals and humans. The glucuronide metabolite M1 and imlunestrant itself were the main drug-related components in human plasma, with M1 adequately qualified in toxicity studies.
In rats, imlunestrant-related radioactivity was almost entirely excreted via faeces, primarily as the unchanged parent compound and, to a lesser extent, as the sulphate conjugate M2. Similarly, in humans, imlunestrant was the predominant component in faeces, with M2 being the most abundant faecal metabolite. Placental transfer and excretion into milk were not investigated.

5.3 Toxicology

Toxicological studies were conducted in rats and monkeys, which are considered appropriate preclinical species based on their pharmacological and pharmacokinetic profiles. Animals were dosed once daily via the oral route, consistent with the proposed clinical use. The duration of the repeat-dose toxicity studies was deemed suitable for a product intended for the treatment of advanced cancer.
In the repeat-dose toxicity studies, imlunestrant-related mortality was observed in rats and was attributed to urinary tract obstruction with ascending inflammation with limited relevance to humans. The primary target organs of imlunestrant in both species were the female reproductive organs, along with rat-specific urinary tract toxicities. These included renal tubular degeneration/regeneration and transitional cell hyperplasia in the urinary bladder at all dose levels. Toxic effects were mostly reversible or showed a tendency to reverse during treatment-free recovery periods, although recovery was only studied in rats. The most relevant in-life findings at tolerated doses were body weight loss and female reproductive toxicity, which were observed at all doses in both species. The adverse effects on the female reproductive system were related to imlunestrant's pharmacological activity. An observed adverse effect level for the effects on female reproductive organs could not be established; the exposures at which these effects occurred were lower than human exposure at therapeutic doses. Adverse effects on male reproductive organs were observed only in rats, with an 8.75-fold safety margin.
Imlunestrant caused embryofoetal lethality and malformations when administered to pregnant rats at clinically relevant exposures. Similar developmental toxicities have been observed with other estrogen-modulating products. The Information for healthcare professionals contains adequate risk mitigation measures, i.e., contraception.
Imlunestrant tested negative for genotoxicity. Carcinogenicity studies were not conducted and are not required under the ICH S9 guideline.
Juvenile toxicity was not assessed, as imlunestrant is intended solely for the treatment of adults.
Imlunestrant demonstrated a potential for phototoxicity *in vivo*, with a safety margin greater than 10-fold compared to human exposure.
There are no concerns regarding excipients or impurities.
The description and evaluation of the findings from the nonclinical studies in the Risk Management Plan (RMP) are considered adequate.
Based on the environmental Risk assessment (ERA), the therapeutic use of imlunestrant in humans is unlikely to pose an environmental risk.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is sufficient to support the approval of Inluriyo with the new active substance imlunestrant in the proposed indication. The pharmacological properties and the pharmacokinetic and toxicity profiles of imlunestrant, were adequately characterised in the nonclinical studies. All nonclinical data relevant to safety have been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

Absorption, distribution, metabolism, elimination

Absorption

Following a single oral dose, imlunestrant reached peak plasma concentrations at approximately 4 hours. The absolute oral bioavailability of the tablet formulation was 10.5% (coefficient of variation 32%).

Administration of the proposed commercial tablet with a low-fat meal resulted in a marked food effect, with a 104% increase in the area under the plasma concentration-time curve (AUC) and a 255% increase in C_{max}. As this increase in exposure is considered clinically relevant, imlunestrant should be administered under fasted conditions, i.e. at least 1 hour after or 2 hours before a meal.

Dose proportionality

The total imlunestrant C_{max} and AUC increased proportionally to the administered dose after administration of single doses and continuous QD dosing between 200 mg and 1200 mg, with no evidence of dose-limited absorption.

Pharmacokinetics after multiple dosing

Following multiple once-daily dosing, an approximately 2- to 3-fold $AUC_{0\text{-}24h}$ accumulation depending on the dose, was observed. For the recommended dose of 400 mg once daily, the accumulation factor was approximately 2.6 after 7 days of treatment (time to steady state), which is consistent with the elimination half-life of imlunestrant.

Distribution

Plasma protein binding was high (>99.9%), independent of concentration and hepatic function, with binding mainly to albumin and α1-acid glycoprotein. The blood-to-plasma ratio was close to 1, indicating similar concentrations in whole blood and plasma.

Pop PK modelling indicated a large central volume of distribution (4312 L in metastatic breast cancer and 2948 L in endometrioid endometrial cancer), consistent with extensive tissue distribution. In breast cancer patients, tumour exposure was approximately 15-fold higher than plasma exposure.

Metabolism and elimination

The parent compound accounted for approximately 19.8% of total circulating entities in plasma. The most abundant metabolites were a glucuronide conjugate (M1; ~19.9%), a sulphate conjugate (M2; ~4.5%), and a mono-oxidised sulphate conjugate (M12; ~4.6%). Additional metabolites were present at low levels, generally around 1% each. The pharmacological activity is mediated by the parent compound, while the identified major metabolites were shown to be pharmacologically inactive.

Oxidative metabolism was primarily mediated by cytochrome P450 (CYP) 3A4/5, with only a marginal contribution from CYP2D6. Glucuronidation was mainly catalysed by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and UGT1A8, with minor involvement of other UGT enzymes. Genetic variation in UGT1A1 did not result in clinically relevant differences in exposure.

Elimination occurred predominantly via the faecal route, with the parent compound representing the major eliminated component (~61.8% of the dose), followed by metabolite M2 (~20.9%). Other metabolites each accounted for less than 5.1% of the dose. Urinary excretion was negligible, accounting for approximately 0.3% of elimination. The mean terminal elimination half-life was approximately 31 hours.

Special populations

Hepatic impairment resulted in increased exposure, with mean AUC increases of 23%, 120% and 206% in mild, moderate and severe impairment, respectively, and a prolonged half-life, while protein binding remained unchanged (>99.9%). A dose reduction to 200 mg once daily is recommended in patients with moderate and severe hepatic impairment.

Population pharmacokinetic analyses showed that mild and moderate renal impairment had no clinically relevant impact on exposure, and no dose adjustment is required; use in severe or end-stage renal impairment is not recommended due to lack of data. Body weight, age and ethnicity did not have a clinically meaningful impact on exposure, and pharmacokinetics were comparable in Chinese subjects and the overall population.

Interactions

Effect of other drugs on imlunestrant

Although identified as a P-glycoprotein (P-gp) substrate in vitro, no clinically relevant effect on exposure was observed in vivo, with unchanged C_{max} and only a marginal decrease in AUC in the presence of a P-gp inhibitor.

Co-administration with a strong CYP3A inhibitor increased exposure by ~90% (C_{max}) and ~112% (AUC), whereas a strong CYP3A inducer decreased exposure by ~29% (C_{max}) and ~42% (AUC). Accordingly, a dose reduction to 200 mg once daily with strong CYP3A inhibitors and consideration of a dose increase to 600 mg once daily with strong CYP3A inducers are recommended.

Protein-binding displacement interactions were not investigated and are considered unlikely to be clinically relevant.

Effect of imlunestrant on other drugs

Clinically relevant increases in exposure were observed for digoxin (P-gp substrate) and rosuvastatin (breast cancer resistance protein substrate), supporting the recommendation for caution when imlunestrant is co-administered with P-gp and breast cancer resistance protein substrates.

Imlunestrant acted as a moderate CYP2D6 inhibitor, increasing dextromethorphan exposure by approximately 30–40%; dose adjustment is not required, but clinical monitoring is recommended.

No clinically relevant interactions were observed with proton pump inhibitors, abemaciclib, aromatase inhibitors or pertuzumab.

Pharmacodynamics

Mechanism of action and primary pharmacology

Imlunestrant is a SERD and antagonist of WT and mutant ERα, inhibiting tumour cell proliferation. Anti-tumour activity was demonstrated in ER-positive breast cancer models, including ESR1-mutant and endocrine-resistant disease, with no clear concentration-dependent effects on estrogen and progesterone receptor depletion.

Secondary pharmacology (safety)

The relationship between imlunestrant plasma concentrations and corrected QT was evaluated at steady state over a dose range of 200 to 1200 mg, covering exposures well above the recommended dose. No concentration-dependent increase in corrected QT was observed, and no cardiac safety concerns were identified. This is consistent with non-clinical findings.

Exposure efficacy/safety relationship

Both progression-free survival (PFS) and the probability of clinical benefit rate (CBR) did not increase significantly with imlunestrant exposure. However, increases in PFS and CBR were observed when imlunestrant was combined with abemaciclib, in the absence of visceral metastases, and in the absence of prior CDK4/6 inhibitor treatment.

Exposure-safety analyses showed a counter-intuitive decrease in the probability of treatment-emergent adverse events (nausea, diarrhoea, and fatigue) with increasing exposure, which was attributed to confounding factors; only prior CDK4/6 inhibitor treatment was associated with an increased risk of nausea.

An effective exposure range of 18–38 ng/mL was defined based on threshold effective concentration for 80% target inhibition, supporting 400 mg once daily as an appropriate dose; higher doses resulted in only a marginal additional increase in exposure, without the expected clinical benefit.

6.2 Dose finding and dose recommendation

The recommended dose of imlunestrant is 400 mg administered orally once daily. Dose selection was based on the phase 1a dose escalation part of the EMBER study employing a standard 3+3 design. The 400 mg dose level was identified as providing sustained plasma exposure while maintaining a favourable tolerability profile compared to higher dose levels, particularly with respect to gastrointestinal toxicity.

6.3 Efficacy

The efficacy of imlunestrant is primarily supported by the randomised, open-label, phase 3 EMBER-3 study comparing imlunestrant monotherapy (Arm A) and imlunestrant plus abemaciclib (Arm C) with standard ET (fulvestrant or exemestane) (Arm B) in patients with ER-positive, HER2-negative advanced or metastatic breast cancer following prior treatment with one line of an AI either as monotherapy or in combination with a CDK4/6 inhibitor.

Eligible patients had experienced a recurrence either during or within the 12 months following completion of adjuvant treatment exclusively with an AI or in combination with a CDK4/6 inhibitor in early breast cancer, or a recurrence more than 12 months after completion of adjuvant treatment followed by disease progression during or after treatment with an AI alone or an AI in combination with a CDK4/6 inhibitor, or they were diagnosed with de novo metastatic disease with progression after treatment with an AI alone or an AI in combination with a CDK4/6 inhibitor.
Randomisation was stratified according to prior treatment with a CDK4/6 inhibitor, presence of visceral metastases and geographic region. ESR1 mutation status was determined using the Guardant360 CDx assay. Premenopausal and perimenopausal women received a gonadotropin-releasing hormone agonist. Treatment was continued until disease progression, treatment discontinuation, or death. The three primary efficacy endpoints were PFS assessed by the investigator in the intent-to-treat (ITT) population, comparing Arm A vs Arm B; PFS assessed by the investigator in the ESR1m-detected population, again comparing Arm A vs Arm B; and PFS assessed by the investigator in the concurrent ITT population, comparing Arm C vs Arm A. Key secondary endpoints were OS in the ITT population, comparing Arm A vs Arm B; OS in patients in the ESR1m-detected population, comparing Arm A vs Arm B; and OS in the concurrent ITT population, comparing Arm C vs Arm A.
The efficacy evaluation focused on comparing imlunestrant monotherapy with ET (Arm A vs Arm B) and on the ESR1-mutated population, in accordance with the requested indication.

EMBER-3 enrolled 874 patients; a total of 323 (37%) patients were ESR1 mutation-positive. Among patients in the monotherapy arms (Arms A and B) with ESR1 mutation-positive disease (n=256), the median age was 61 years (range: 28–85 years), and all patients were female. The ethnic distribution was 61% White, 26% Asian, 4% Black, 4% American Indian or Alaska Native, and 19% Hispanic or Latino. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 at baseline. Most patients had visceral metastases (59%) at study entry, 23% had stage IIIB/IIIC disease, 12% had lobular breast cancer, and 14% were premenopausal. Of the enrolled patients, 21% received imlunestrant as first-line treatment for metastatic breast cancer, whereas 79% received it as second-line treatment in the metastatic setting. Overall, 70% of patients had prior exposure to a CDK4/6 inhibitor, including 2% in the adjuvant setting and 67% in the metastatic setting.
At the data cut-off (DCO) of the PFS final analysis (24 June 2024), the study demonstrated a statistically significant improvement in PFS with imlunestrant compared to ET in the ESR1-mutated population, with a median PFS of 5.5 months (95% CI 3.9-7.4) versus 3.8 months (95% CI 3.7-5.5) and a hazard ratio of 0.62 (95% CI 0.46,0.82; p=0.0008). The Kaplan-Meier curves separated at around 4 months and remained separated throughout follow-up. These findings were consistent across updated analyses with extended follow-up.
It is noteworthy that statistical significance for the other primary endpoint – PFS in the ITT – was not met at the final analysis, leading to the applicant restricting the proposed indication to the ESR1-m-detected population.

At DCO of interim analysis 3, (OS) analyses demonstrated a clinically meaningful benefit for imlunestrant compared to the control arm in the ESR1-mutated population, with a hazard ratio of 0.60 (95% CI 0.43-0.86) at the most recent interim analysis, although statistical significance was not reached. The Kaplan-Meier curves show a sustained separation over time.
The robustness of the efficacy conclusions is limited by multiple factors, including the open-label design of the study, the use of investigator-assessed PFS as primary endpoint the absence of ESR1 mutation status as a stratification factor. Notwithstanding these limitations, the consistency of OS results provides supportive evidence of clinical benefit in the female ESR1-mutated population. As no male patients were included in the ESR1 mutation-positive population, the indication was restricted to the female population.

6.4 Safety

The safety profile of imlunestrant was primarily characterised in the EMBER-3 study and is considered acceptable within the context of advanced breast cancer. The most frequently reported adverse events included fatigue, diarrhoea and nausea. The incidence of grade ≥3 AEs, serious adverse events, and fatal adverse events was comparable between treatment arms. Please refer to the attached Information for healthcare professionals for further information.

6.5 Final clinical benefit risk assessment

The EMBER-3 study demonstrated a statistically significant improvement in PFS in patients with ESR1-mutated ER-positive, HER2-negative advanced breast cancer; however, the magnitude of the benefit is modest and associated with methodological limitations, including the open-label design and uncertainties related to endpoint assessment.
OS results, although not statistically significant at interim analyses, consistently demonstrated a clinically meaningful benefit, supported by sustained separation of survival curves. The safety profile of imlunestrant was considered acceptable overall and comparable to available ETs.
Despite residual uncertainties related to study design and the limited magnitude of PFS benefit, the totality of the evidence, in particular the consistent and clinically meaningful OS findings, supports a positive benefit-risk balance in a population with an unmet medical need. Final OS results will be provided as a post-authorisation requirement.

7 Risk management plan summary

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

8 Appendix

Approved Information for healthcare professionals

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

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

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

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.*

INLURIYO®

Composition

Active substances

Imlunestrant as imlunestrant tosylate

Excipients

Tablet core:

croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, cellulose microcrystalline.

Film-coating

Macrogols 4000, polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

A 200 mg film-coated tablet contains ca. 3.0 mg of sodium (as croscarmellose sodium).

Pharmaceutical form and active substance quantity per unit

Imlunestrant film-coated tablets 200 mg:

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

White, oval tablet debossed with “Lilly” on one side and “1717” and an elongated 4-point starburst on the other side.

Indications/Uses

Inluriyo is indicated as monotherapy for the treatment of adult female patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 (ESR1)-mutated, advanced or metastatic breast cancer, who have disease progression following prior treatment with an endocrine based regimen.

In pre- or perimenopausal women, Inluriyo should be combined with an LHRH agonist (LHRH = Luteinising Hormone Releasing Hormone).

Dosage/Administration

Posology

Treatment must be initiated by a physician experienced in the use of anticancer therapies.

The selection of patients with ER-positive, HER2-negative advanced breast cancer for treatment with Inluriyo must be based on the detection of an activating ESR1 mutation carried out with a validated test in plasma samples (see «Clinical efficacy»).

The recommended dose of imlunestrant as a single agent is 400 mg orally (two 200 mg tablets), once daily.

Treatment should be continued, as long as a clinical benefit is observed 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, Inluriyo should be taken at the usual time.

Vomiting

If the patient vomits after taking the Inluriyo 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, decrease the dose by 200 mg. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-2. Discontinue Inluriyo for patients unable to tolerate 200 mg once daily.

Table 1: Recommended Dose Modification for Hepatotoxicity

Monitor alanine aminotransferase (ALT)/aspartate aminotransferase (AST) during Inluriyo therapy as clinically indicated.	
Toxicity [a]	**Inluriyo Dose Modifications**
Persistent or Recurrent: AST/ALT >3.0-5.0 × upper limit of normal (ULN)	Suspend until toxicity resolves to baseline or to >ULN-3.0×ULN. Dose reduction is not required.
If AST/ALT at baseline is within the normal range: AST/ALT >5.0-20×ULN **Or** If AST/ALT at baseline is above ULN:	Suspend until toxicity resolves to baseline or to >ULN-3.0×ULN. Resume at next lower dose level.

AST/ALT ≥3 × baseline (if AST/ALT ≥1.5 x ULN at baseline) or AST/ALT >8 × ULN (whichever is the lower threshold)	
AST/ALT >20.0×ULN **Or** ALT/AST ≥3 × ULN concurrent with total bilirubin (TBL) ≥2 × ULN (if ALT/AST <1.5 × ULN at baseline), in the absence of cholestasis **Or** ALT/AST ≥2 × baseline concurrent with TBL ≥2 × ULN (if ALT or AST ≥1.5 × ULN at baseline), in the absence of cholestasis	Discontinue Inluriyo.

Table 2: Recommended Dose Modification for Adverse Reactions (except hepatotoxicity)

Toxicity [a]	**Inluriyo 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 or 4 (except non-hepatic asymptomatic laboratory changes)	Suspend until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose level.

[a] NCI CTCAE

Strong CYP3A Inhibitors

Concomitant use of strong CYP3A inhibitors should be avoided. If strong CYP3A inhibitors cannot be avoided, the imlunestrant dose should be reduced by 200 mg once daily (see section «Interactions»).

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 «Interactions»).

Special Populations

Elderly

No dose adjustment is required on the basis of patient age (see section «Pharmacokinetic properties»).

Hepatic impairment

Reduce the Inluriyo dose to 200 mg once daily in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. There are no data regarding Inluriyo administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section «Pharmacokinetic properties»).

Paediatric population

The safety and efficacy of Inluriyo in children from birth to 18 years of age has not been established. No data are available.

Mode of administration

Inluriyo is for oral use.

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

Take on an empty stomach at least 1 hour before or 2 hours after food (see section «Pharmacokinetic properties»). The tablets should be swallowed whole (patients should not split, crush, or chew the tablets before swallowing).

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Embryofetal toxicity

Imlunestrant can cause embryofetal toxicity when administered during pregnancy based on its mechanism of action and findings from toxicity studies in animals. A pregnancy test must be performed prior to starting imlunestrant therapy, and highly effective contraception should be used during treatment and for at least 1 week after the last dose (see section «Pregnancy, lactation»).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially “sodium-free”.

Interactions

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

Potential for other medicinal products to affect imlunestrant

Strong CYP3A inhibitors

Coadministration of imlunestrant with itraconazole (a strong CYP3A inhibitor) increased the AUC and C_{max} of imlunestrant by 111% and 87%, 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 «Posology»).

Strong CYP3A inducers

Coadministration of imlunestrant with carbamazepine (a strong CYP3A inducer) decreased the AUC and 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 «Posology»).

Gastric 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 affect other medicinal products

CYP2D6 substrates

Imlunestrant increased the AUC and C_{max} of dextromethorphan (a CYP2D6 substrate) by 33% and 43%, respectively. Use caution 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 39% and 60%, respectively. Use caution 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 49% and 65%, respectively. Use caution when coadministering imlunestrant with BCRP substrates for which a small increase in concentration leads to significant adverse events.

In vitro studies

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.

Effect of imlunestrant on other drugs

Imlunestrant had no clinically meaningful effect on the pharmacokinetics of midazolam (a CYP3A substrate) or repaglinide (a CYP2C8 substrate).

Imlunestrant increased the Cmax of omeprazole (a CYP2C19 substrate) by 28%. No changes in omeprazole AUC were observed.

Pregnancy, lactation

Inluriyo should be avoided during pregnancy and in women of childbearing potential not using contraception. Based on the mechanism of action of imlunestrant and findings from toxicity studies in animals, Inluriyo can cause foetal harm when administered to pregnant women. Females of reproductive potential should be advised to use highly effective contraception during treatment with Inluriyo and for at least 1 week after the last dose (see section «Warnings and precautions» and

«Preclinical safety data»).

Pregnancy

Inluriyo should not be used during pregnancy. There are no data from the use of imlunestrant in pregnant women. Studies in animals have shown embryofoetal toxicity (see section «Preclinical safety data»). The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Inluriyo. If pregnancy occurs while taking Inluriyo, 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, it is recommended that lactating women should not breast-feed during treatment with Inluriyo and at least 1 week after the last dose of Inluriyo.

Fertility

Based on findings from animal studies (see section «Preclinical safety data») and its mechanism of action, Inluriyo may impair fertility in females.

Effects on the ability to drive and use machines

Inluriyo has influence on the ability to drive and use machines. Because fatigue, arthralgia, nausea, and headaches have been reported in patients treated with Inluriyo (see «Undesirable effects»), patients affected by these undesirable effects must exercise caution when driving or operating machines.

Undesirable effects

Summary of the safety profile

The most common adverse reactions with Inluriyo monotherapy (≥10%) were ALT increased, AST increased, joint and musculoskeletal pain, fatigue, diarrhoea, nausea, triglycerides increased and back pain. The most common Grade ≥3 (≥1%) adverse reactions were joint and musculoskeletal pain. No serious adverse reactions were reported in ≥1% of patients.

Adverse reactions leading to discontinuations of Inluriyo monotherapy, not including discontinuations due to fatal adverse reactions, were ALT increased (0.9%), abdominal pain and fatigue (each 0.3%).

Adverse reactions leading to dose reductions of Inluriyo monotherapy included AST increased (0.6%), ALT increased, fatigue, nausea, and vomiting (each 0.3%).

Adverse reactions leading to dose interruption of Inluriyo monotherapy in ≥1% of patients included vomiting.

List of adverse reactions

The integrated frequency and severity of adverse drug reactions reported in patients treated with 400 mg Inluriyo once daily from a randomized, open-label, multicenter Phase 3 study (EMBER-3) (N=327) and an open-label, multicenter, dose escalation and dose expansion phase 1a/1b study (EMBER) (N=208) are presented in the following list.

In the following list, 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.

Adverse Drug Reactions in Patients Receiving Imlunestrant (400 mg, Once Daily), EMBER-3 and EMBER (N: 378)

Metabolism and nutrition disorders

Common: Decreased appetite[a]

Nervous system disorders

Common: Headache

Vascular disorders

Common: Hot flush[a]

Respiratory, thoracic and mediastinal disorders

Common: Cough[a]

Gastrointestinal disorders

Very common: Diarrhoea (22.5%), Nausea (20.1%),

Common: Abdominal pain[a], Constipation, Vomiting.

Hepatobiliary Disorders

Very common: Alanine aminotransferase increased[b] (34.3%), Aspartate aminotransferase increased[b] (33.2%), Triglycerides increased[b] (21%).

Musculoskeletal and connective tissue disorders

Very common: Joint and musculoskeletal pain[a] (23.2%), Back pain (10.3%)

General disorders and administration site conditions

Very common: Fatigue[a] (25.7%)

[a] Consolidated term. The Preferred Terms included in each consolidated term are as follows:

- Abdominal pain (abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal rigidity, abdominal tenderness, epigastric discomfort, gastrointestinal pain)
- Cough (cough, productive cough)
- Decreased appetite (decreased appetite, early satiety)
- Fatigue (fatigue, asthenia, lethargy, malaise)
- Hot flush (flushing, hot flush)
- Infections (Includes all reported preferred terms that are part of the Infections and Infestations System Organ Class)
- Joint and musculoskeletal pain (arthralgia, myalgia, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, pain in extremity, neck pain)
- Rash (dermatitis acneiform, drug eruption, erythema multiforme, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular)

[b] Based on laboratory assessments

Elderly

Inluriyo has been studied in 211 patients aged greater than or equal to 65 years, including 65 patients aged ≥75 years. No clinically meaningful differences in safety profile were observed in elderly patients compared to non elderly patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, use supportive therapy. There is no known antidote for imlunestrant overdose.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

Imlunestrant is an orally bioavailable potent selective degrader and complete antagonist of wild-type and mutant estrogen receptor α (ERα). In in vitro studies, imlunestrant antagonized and degraded wild-type and mutant ERα, leading to inhibition of estrogen receptor-dependent gene transcription and cellular proliferation in ER+ breast cancer cells. In in vivo studies, imlunestrant exhibited continuous estrogen receptor (ER) antagonism throughout the dosing period, intratumoural accumulation relative to plasma, and brain penetration. Imlunestrant demonstrated anti-tumour activity in multiple ER+ breast cancer xenograft models, including models with ESR1 mutations, and models with resistance to fulvestrant and CDK4/6 inhibitors. Consistent with its profile as a complete antagonist, imlunestrant displayed no uterotrophic activity in an immature rat model.

Pharmacodynamics

Cardiac Electrophysiology

The effect of imlunestrant on the QTc interval was evaluated in 79 patients with matching PK and QTcF samples from EMBER. Imlunestrant concentrations across the 200 mg to 1200 mg dose range had no clinically meaningful effect on QTc interval (that is, >10 ms). At 3 times the recommended dose, clinically significant QTc interval prolongation was not observed.

Clinical efficacy

The efficacy of INLURIYO monotherapy was evaluated in EMBER-3, a randomized, open-label, active-controlled, multicenter trial that enrolled adult patients with ER+, HER2- locally advanced or metastatic breast cancer (MBC), who were previously treated with an aromatase inhibitor either alone or in combination with a CDK 4/6 inhibitor. 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.

A total of 874 patients were randomized 1:1:1 between 3 treatment arms:

- Arm A (N=331): INLURIYO 400 mg orally, once daily
- Arm B (N=330): Standard of Care (SOC) which included Investigator's Choice of Endocrine Therapy (fulvestrant 500 mg IM or exemestane 25 mg orally, once daily)
- Arm C (N=213): INLURIYO 400 mg orally, once daily + Abemaciclib 150 mg orally, twice daily

Most patients, 64% (N=561), were enrolled following locally advanced or metastatic disease progression while on or after treatment with an AI alone or in combination with a CDK 4/6i (59%). 32% (N=282) of patients were enrolled after disease recurrence while receiving, or within 12-months of completing adjuvant endocrine therapy (ET) with an aromatase inhibitor (AI) alone or in combination with a CDK 4/6 inhibitor.

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). *ESR1*m status was detected using the Guardant360 CDx assay. Pre/perimenopausal women and men enrolled in the study were administered the gonadotropin-releasing hormone agonist for at least 4 weeks prior to and for the duration of EMBER-3. Patients were treated until disease progression, treatment discontinuation, or death.

The primary endpoint for EMBER-3 was progression-free survival (PFS) as assessed by the investigator and was tested for the following comparisons: Arm A versus Arm B in the intent to treat population (ITT); Arm A versus Arm B in the ESR1m sub-population, and Arm C versus Arm A in a concurrent ITT population. Other efficacy endpoints included overall survival (OS).

Among the patients in the monotherapy arms (Arms A and B) who were positive for *ESR1*m (N=256), the median age was 61 years (range: 28-85 years); all patients were female; 61% were White, 26% Asian, 4% Black, 4% were American Indian or Alaskan Native and 19% were Hispanic/Latino. All patients were required to have a baseline ECOG performance status of 0 or 1. Most patients had visceral metastasis (59%) at baseline, 2% had stage IIIB/IIIC disease, 9% had lobular breast cancer and 11% were pre-menopausal. Of the patients enrolled, 21% were treated with INLURIYO in 1L MBC and 79% were treated in 2L MBC. Overall, 70% of patients were treated with a prior CDK 4/6i, 2% treated in the adjuvant setting and 67% treated in the MBC setting.

The efficacy results from these patients are summarized in Table 3. At the primary analysis (24 June 2024 cut-off), there was a statistically significant difference in investigator-assessed PFS for INLURIYO compared to SOC (fulvestrant or exemestane).

Table 3: 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)	102 (86.4)
Median PFS, months (95% CI)*	5.5 (3.9, 7.4)	3.8 (3.7, 5.5)
Hazard Ratio (95% CI)**	0.62 (0.46, 0.82)	
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).

At the third interim analysis of OS (data cut-off 18 August 2025), a total of 128 OS events were observed in the two ESR1m-positive arms (57 in Arm A and 71 in Arm B). The HR was 0.60 (95% CI: 0.43, 0.86) (not statistically significant).

Pharmacokinetics

Absorption

The steady-state mean (%CV) maximum concentration (C_{max}) of imlunestrant is 141 ng/mL (45%) and the area under the concentration-time curve (AUC_{0-24h}) is 2400 ng*h/mL (46%) after administration of the recommended dosage of 400 mg once daily. The C_{max} and AUC of imlunestrant increase proportionally over a dosage range from 200 mg to 1200 mg once daily (0.5 to 3 times the approved recommended dosage).

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 (tmax) 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 255% and $AUC_{(0-\infty)}$ by 104% compared to fasted administration. Imlunestrant exposures in the presence of a high-fat meal are unknown.

Distribution

The mean (CV%) apparent central volume of distribution of imlunestrant is 4310 L (69%) in patients with advanced or metastatic breast cancer. Human protein binding of imlunestrant is 99.93 to 99.96% and independent of concentration.

Metabolism

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

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 radiolabeled dose of imlunestrant 400 mg to healthy subjects, 97.3% of the dose was recovered in feces and 0.278% in urine.

Kinetics in specific patient groups

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 significant differences in the pharmacokinetics of imlunestrant in subjects with mild hepatic impairment (Child-Pugh A). The AUC of imlunestrant increased by 122% in subjects with moderate hepatic impairment (Child-Pugh B) and dose-normalized AUC increased by 206% 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) and patients on dialysis on pharmacokinetics of imlunestrant is unknown.

Preclinical data

Repeat-dose studies were conducted in rats and cynomolgus monkeys to characterize toxicity. Important effects included pharmacologically mediated female reproductive tract toxicity at all doses tested, and effects in other organs sensitive to hormones such as the mammary gland and testes. Other important effects were anatomic changes in the urinary tract, and minimal to mild ocular lens fiber degeneration. There were no adverse non-reproductive findings at any dose in cynomolgus monkeys. In rats, imlunestrant produced no adverse non-reproductive effects at exposures of approximately 4-fold the systemic exposure ($AUC_{0\text{-}24hr}$) achieved in humans receiving the recommended dose of 400 mg/day.

Genotoxicity/Carcinogenicity

Imlunestrant does not pose a biologically relevant genotoxic risk. Imlunestrant was not mutagenic in the bacterial reverse mutation assay. Imlunestrant was positive in the in vitro micronucleus assay but did not cause chromosomal damage or DNA strand breaks in vivo when tested up to 2000 mg/kg in the rat comet and bone marrow micronucleus assays.

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 tumors (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 tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Embryofetal toxicity/Teratogenicity

Based on findings in animals and its mechanism of action, imlunestrant can cause fetal harm when administered during pregnancy. In animal studies, administration of imlunestrant to pregnant rats during the period of organogenesis led to maternal toxicity, early delivery, embryo lethality, and teratogenic foetal effects at maternal exposures lower than the human therapeutic exposure.

Fertility

Based on its mechanism of action and findings from repeat-dose toxicity studies, imlunestrant may impair fertility. In animals, imlunestrant was associated with reversible cessation of estrous cycling and generally reversible anatomic effects on the female and male reproductive tract.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

Authorisation number

70233 (Swissmedic)

Packs

Inluriyo 200 mg pack: 28 and 56 film-coated tablets (B)

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE.

Date of revision of the text

November 2025