

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218881Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INLURIYO safely and effectively. See full prescribing information for INLURIYO.

INLURIYO (imlunestrant) tablets, for oral use

Initial U.S. Approval: 2025

INDICATIONS AND USAGE

INLURIYO™ is an estrogen receptor antagonist indicated for:

- treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy (1)

DOSAGE AND ADMINISTRATION

- Select patients for treatment based on the presence of *ESR1* mutations. (2.1)
- The recommended dosage is 400 mg orally once daily, on an empty stomach. (2.2)
- Reduce the dose in patients with moderate or severe hepatic impairment (2.4, 8.6)
- Dosage modifications may be required. (2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg of imlunestrant. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- **Embryo-Fetal Toxicity:** INLURIYO can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.1, 8.1, 8.3)

ADVERSE REACTIONS

The most common (incidence $\geq 10\%$) adverse reactions, including laboratory abnormalities were: hemoglobin decreased, musculoskeletal pain, calcium decreased, neutrophils decreased, AST increased, fatigue, diarrhea, ALT increased, triglycerides increased, nausea, platelets decreased, constipation, cholesterol increased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Strong CYP3A Inhibitors:** Avoid concomitant use with INLURIYO. If concomitant use cannot be avoided, decrease the INLURIYO dosage. (2.5, 7.1)
- **Strong CYP3A Inducers:** Avoid concomitant use with INLURIYO. If concomitant use cannot be avoided, increase the INLURIYO dosage (2.5, 7.1).

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INLURIYO is indicated for the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *estrogen receptor-1 (ESR1)*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment of ER-positive, HER2-negative advanced or metastatic breast cancer with INLURIYO based on the presence of *ESR1* mutation(s) in a plasma specimen using an FDA-approved test [see *Indications and Usage (1) and Clinical Studies (14.1)*].

Information on FDA-approved tests for the detection of *ESR1* mutations in breast cancer is available at:

<https://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage and Administration

The recommended dosage of INLURIYO is 400 mg orally once daily until disease progression or unacceptable toxicity.

Take on an empty stomach at least 2 hours before food, or 1 hour after food [see *Clinical Pharmacology (12.3)*]. Take INLURIYO tablets at approximately the same time daily. Swallow the tablets whole. Do not split, crush, or chew the tablets.

Pre/perimenopausal women and men should receive a gonadotropin-releasing hormone agonist (GnRH) according to current clinical practice standards.

If patient misses a dose by 6 or more hours or vomits, instruct the patient to take the next dose the following day at its scheduled time.

2.3 Dosage Modifications for Adverse Reactions

The recommended INLURIYO dosage modifications for adverse reactions are provided in Tables 1 and 2.

The recommended dose reduction is to 200 mg once daily.

Permanently discontinue INLURIYO in patients who are unable to tolerate 200 mg once daily.

Table 1: INLURIYO Dosage Modification - Adverse Reactions (except hepatotoxicity)

| Grade | INLURIYO Dosage 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 \leq Grade 1. Resume INLURIYO at the same dose level. |
| Grade 3 or 4 (except non-hepatic asymptomatic laboratory changes) | Suspend until toxicity resolves to baseline or \leq Grade 1. Resume INLURIYO at next lower dose level. |

Table 2: INLURIYO Dosage Modification - Hepatotoxicity

| Monitor alanine aminotransferase (ALT)/aspartate aminotransferase (AST) during imlunestrant therapy as clinically indicated. | |
|--|---|
| Liver Transaminase | INLURIYO Dosage Modifications |
| Persistent or Recurrent: AST/ALT >3.0 - $5.0 \times$ ULN | Suspend until toxicity resolves to baseline or to $>$ ULN- $3.0 \times$ ULN. Resume INLURIYO at the same dose level. |

| | |
|---|---|
| <p>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: AST/ALT ≥3 × baseline (if AST/ALT ≥1.5 × ULN at baseline) Or AST/ALT >8 × ULN (whichever is the lower threshold)</p> | <p>Suspend until toxicity resolves to baseline or to >ULN-3.0×ULN. Resume INLURIYO at next lower dose level or discontinue if receiving 200 mg daily.</p> |
| <p>AST/ALT >20.0×ULN Or ALT or AST ≥ 3 × ULN concurrent with TBL ≥ 2 × ULN (if ALT or AST < 1.5 × ULN at baseline), in the absence of cholestasis Or ALT or AST ≥ 2 × baseline concurrent with TBL ≥ 2 × ULN (if ALT or AST ≥ 1.5 × ULN at baseline), in the absence of cholestasis</p> | <p>Discontinue INLURIYO.</p> |

Abbreviation: ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBL=total bilirubin, ULN = upper limit of normal.

2.4 Dosage in Patients with Hepatic Impairment

The recommended dosage of INLURIYO for patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is 200 mg once daily. Monitor for increased adverse reactions [see *Clinical Pharmacology (12.3)*].

2.5 Dosage Modifications for Drug Interactions

Strong CYP3A Inhibitors

Avoid concomitant use with strong CYP3A inhibitors. If concomitant use cannot be avoided, decrease the INLURIYO dosage to 200 mg once daily [see *Drug Interactions (7.1)*].

Strong CYP3A Inducers

Avoid concomitant use with strong CYP3A inducers. If concomitant use cannot be avoided, increase the INLURIYO dosage to 600 mg once daily [see *Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

INLURIYO tablets contain 200 mg imlunestrant and are white, film coated-capsule-shaped tablets, with “LILLY” on one side and “1717” and elongated 4-point starburst on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, INLURIYO can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of imlunestrant to pregnant rats during the period of organogenesis led to embryo-fetal mortality and structural abnormalities at maternal exposures that were below the human exposure at the recommended dose based on AUC.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose [see *Use in Specific Populations (8.1, 8.3)* and *Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of INLURIYO was evaluated in 651 patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with endocrine therapy with or without a prior CDK4/6 inhibitor in EMBER-3 [see *Clinical Studies (14.1)*]. Patients received INLURIYO 400 mg orally, once daily (n=327), or standard of care (n=324) consisting of either fulvestrant (n=292) or exemestane (n=32). Among patients who were treated with INLURIYO, the median duration of exposure was 5.6 months (range: 0.2 to 28.6 months) in EMBER-3.

Serious adverse reactions occurred in 10% of patients who received INLURIYO. Serious adverse reactions in > 1% of patients included pleural effusion (1.2%). Fatal adverse reactions occurred in 1.8% of patients who received INLURIYO, including cardiac arrest, acute myocardial infarction, right ventricular failure, hypovolemic shock, and upper gastrointestinal hemorrhage (each 0.3%).

Permanent treatment discontinuation of INLURIYO due to an adverse reaction occurred in 4.6% of patients. Adverse reactions which resulted in permanent discontinuation of INLURIYO included increased alanine aminotransferase (0.9%), abdominal pain, fatigue, fractured sacrum, hepatotoxicity, neuropathy peripheral, and pyrexia (each 0.3%).

Dosage interruption of INLURIYO due to an adverse reaction occurred in 10% of patients. Adverse reactions which required dosage interruption in >0.5% were vomiting (1.5%); increased aspartate aminotransferase and COVID-19 (each 0.9%); and increased alanine aminotransferase, anemia, diarrhea, decreased neutrophil count, and pyrexia (each 0.6%).

Dose reductions of INLURIYO due to an adverse reaction occurred in 2.4% of patients. Adverse reactions which required dose reductions were increased aspartate aminotransferase (0.6%); and increased alanine aminotransferase, anemia, fatigue, interstitial lung disease, nausea, neutropenia, and vomiting (each 0.3%).

The most common (≥10%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased, musculoskeletal pain, calcium decreased, neutrophils decreased, AST increased, fatigue, diarrhea, ALT increased, triglycerides increased, nausea, platelets decreased, constipation, cholesterol increased, and abdominal pain.

Table 3 summarizes the adverse reactions in EMBER-3.

Table 3: Adverse Reactions (≥10%) in Patients Who Received INLURIYO in EMBER-3

| Adverse Reaction ^a | INLURIYO N=327 | | Fulvestrant or Exemestane N=324 | |
|---|-------------------|--------------------|------------------------------------|--------------------|
| | All Grades % | Grades 3 or 4 % | All Grades % | Grades 3 or 4 % |
| Musculoskeletal Disorders | | | | |
| Musculoskeletal Pain | 30 | 3.7 | 29 | 1.9 |
| General Disorders and Administration Site Conditions | | | | |
| Fatigue ^b | 23 | 0.3 | 14 | 0.6 |
| Gastrointestinal Disorders | | | | |
| Diarrhea | 22 | 0.6 | 12 | 0.0 |
| Nausea | 17 | 0.3 | 13 | 0.0 |
| Constipation | 10 | 0 | 6 | 0.3 |
| Abdominal pain ^b | 10 | 0.3 | 6 | 0.6 |

^a Adverse reactions were graded using NCI CTCAE version 5.0.

^b Includes other related terms

Clinically relevant adverse reactions (<10%) in patients who received INLURIYO included: vomiting (9%), headache (9%), cough (9%), decreased appetite (8%), hot flush (7%), pruritus (3.7%), dyspepsia (2.8%), and stomatitis (2.4%).

Table 4 summarizes the laboratory abnormalities in EMBER-3.

Table 4: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients Who Received INLURIYO in EMBER-3

| Lab Abnormality ^a | INLURIYO ^b | | Fulvestrant or Exemestane ^b | |
|--------------------------------------|-----------------------|-----------------|--|-----------------|
| | All Grades % | Grades 3 or 4 % | All Grades % | Grades 3 or 4 % |
| Hematology | | | | |
| Hemoglobin decreased | 30 | 1.2 | 35 | 3.4 |
| Neutrophils decreased | 26 | 4 | 29 | 4.7 |
| Platelets decreased | 16 | 1.8 | 14 | 1.3 |
| Chemistry | | | | |
| Calcium decreased | 26 | 0 | 19 | 0.6 |
| Aspartate aminotransferase increased | 25 | 1.9 | 27 | 2.3 |
| Alanine aminotransferase increased | 21 | 1.3 | 23 | 1.0 |
| Triglycerides increased | 21 | 0 | 22 | 1.2 |
| Cholesterol increased | 10 | 0 | 12 | 0 |

^a Graded according to NCI CTCAE version 5

^b The denominator used to calculate the rate varied from 252 to 325 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on INLURIYO

Strong CYP3A Inhibitors

Avoid concomitant use of INLURIYO with strong CYP3A inhibitors. If concomitant use cannot be avoided, reduce the dosage of INLURIYO [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

Imlunestrant is a CYP3A substrate. Concomitant use of a strong CYP3A inhibitor increases imlunestrant exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of INLURIYO-associated adverse reactions.

Strong CYP3A Inducers

Avoid concomitant use of INLURIYO with strong CYP3A inducers. If concomitant use cannot be avoided, increase the dosage of INLURIYO [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

Imlunestrant is a CYP3A substrate. Concomitant use of a strong CYP3A inducer decreases imlunestrant exposure [see *Clinical Pharmacology (12.3)*], which may reduce effectiveness of INLURIYO.

7.2 Effects of INLURIYO on Other Drugs

P-gp or BCRP Substrates

Avoid concomitant use unless otherwise recommended in the Prescribing Information for P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse reactions.

Imlunestrant inhibits both P-gp and BCRP. Imlunestrant increases exposure of P-gp and BCRP substrates, which may increase the risk of adverse reactions related to these substrates [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, INLURIYO can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available human data on INLURIYO use in pregnant women to inform the drug-associated risk. In an animal reproduction study, oral administration of imlunestrant to pregnant

rats during the period of organogenesis led to embryo-fetal mortality and structural abnormalities at maternal exposures below the human exposure at the recommended dose based on AUC (*see Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development study, imlunestrant was administered orally to pregnant rats during the period of organogenesis from gestation day 6 to 17 at doses of 0.3, 3, and 30 mg/kg/day. Imlunestrant caused embryo-fetal mortality (increased resorption, reduced number of live fetuses) at ≥ 0.3 mg/kg/day, approximately 0.1 times the human AUC at the recommended dose. Early delivery, fetal malformations (including small jaw, protruding tongue, malrotated, and hyperextended hindlimb) and fetal variations (edema localized subcutis) were observed at ≥ 3 mg/kg/day, approximately 1 time the human AUC at the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of imlunestrant or its metabolites in human milk, its effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise lactating women to not breastfeed during treatment with INLURIYO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

INLURIYO can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating INLURIYO.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose.

Infertility

Based on findings in animals, INLURIYO may impair fertility in females and males of reproductive potential. Findings in animals were reversible [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of INLURIYO have not been established in pediatric patients.

8.5 Geriatric Use

Of 327 patients who received INLURIYO in the EMBER-3 study, 118 patients were ≥ 65 years of age and 37 patients were ≥ 75 years of age. No overall differences in safety or effectiveness of INLURIYO have been observed between patients 65 years of age and older and younger adult patients.

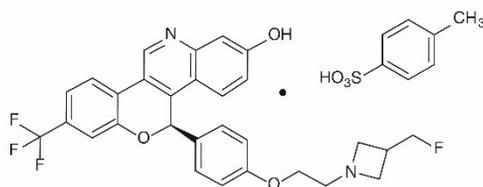
8.6 Hepatic Impairment

Reduce the dose of INLURIYO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dosage modification is recommended for patients with mild hepatic impairment (Child-Pugh A) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

11 DESCRIPTION

INLURIYO tablets contain imlunestrant, an estrogen receptor antagonist. The chemical name for imlunestrant tosylate is (5R)-5-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-8-(trifluoromethyl)-5H-(1)benzopyrano(4,3-c)quinolin-2-ol,

tosylate salt (1:1). Imlunestrant tosylate is a white to practically white to yellow powder with the empirical formula $C_{29}H_{24}F_4N_2O_3 \cdot C_7H_8O_3S$ and a molecular weight 696.71 g/mol. The aqueous solubility of imlunestrant tosylate is slightly soluble at low pH, insoluble at neutral pH, and sparingly soluble at high pH. The chemical structure of imlunestrant tosylate is shown below:



INLURIYO are tablets for oral administration. Each INLURIYO tablet is available as capsule-shaped, film-coated tablet that contains 200 mg imlunestrant (equivalent to 265.66 mg imlunestrant tosylate). The tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose. The tablets are coated using a common white coating, which consists of polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Imlunestrant is an estrogen receptor (ER) antagonist that binds to ER α . In vitro, imlunestrant induced degradation of ER α , leading to inhibition of ER-dependent gene transcription and cellular proliferation in ER+ breast cancer cells. Imlunestrant demonstrated in vitro and in vivo anti-tumor activity in ER+ breast cancer xenograft models, including models with *ESR1* mutations.

12.2 Pharmacodynamics

Imlunestrant exposure-response relationships and the time course of pharmacodynamics have not been fully characterized.

Cardiac Electrophysiology

At 2 times the mean maximum concentration observed with the approved recommended dose, a mean increase in the QTc interval >20 msec was not observed.

12.3 Pharmacokinetics

Imlunestrant pharmacokinetics were observed at steady state at the approved recommended dosage and are presented as mean (%CV) unless otherwise specified. The maximum concentration (C_{max}) of imlunestrant is 141 ng/mL (45%) and the area under the concentration-time curve (AUC) is 2,400 ng*h/mL (46%). Imlunestrant C_{max} and AUC increase in a dose proportional manner over a dosage range of 200 mg to 1,200 mg (0.5 to 3 times the approved recommended dosage) once daily. Steady-state is reached in approximately 6 days and the accumulation is 2.3-fold based on AUC.

Absorption

Imlunestrant absolute oral bioavailability after a single oral 400 mg dose is 10% (32%). Imlunestrant median (min, max) time to maximum plasma concentration (T_{max}) is 4 (2, 8) hours.

Effect of Food

Imlunestrant AUC increased 2-fold and C_{max} increased 3.6-fold following administration with a low-fat meal (approximately 475 calories with 13% fat, 16% protein, and 71% carbohydrates). The effect of high-fat meal (approximately 800-1,000 calories with 500-600 calories from fat) on imlunestrant exposures is unknown.

Distribution

The apparent (oral) volume of distribution is 8,120 L (69%). Imlunestrant protein binding is >99% and is not concentration dependent.

Elimination

Imlunestrant elimination half-life is 30 hours with an estimated apparent clearance of 166 L/h (51%).

Metabolism

Imlunestrant is metabolized by sulfation, CYP3A4, and direct glucuronidation (UGT1A1, 1A3, 1A8, 1A9, 1A10).

Excretion

After a single dose of radiolabeled imlunestrant 400 mg to healthy subjects, 97% of the dose was recovered in feces (62% unchanged) and 0.3% in urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of imlunestrant based on age (28 to 95 years), race (64% White, 23% Asian, and 5% Black or African American), ethnicity (74% non-Hispanic/Latino, 17% Hispanic/Latino), body weight (36 to 145 kg), mild to moderate (eGFR 30 to 89 mL/min, estimated by CKD-EPI equation) renal impairment, or UGT1A1 genetic polymorphisms (e.g., UGT1A1*1/*28 or UGT1A1*28/*28). The effect of severe (eGFR 15 to 29 mL/min) renal impairment and renal impairment requiring dialysis on imlunestrant pharmacokinetics is unknown.

Patients with Hepatic Impairment

Imlunestrant AUC increased 2.2-fold in subjects with moderate hepatic impairment (Child-Pugh B) and 3.1-fold in subjects with severe hepatic impairment (Child-Pugh C). No clinically significant differences in the pharmacokinetics of imlunestrant were observed in subjects with mild hepatic impairment (Child-Pugh A).

Drug Interaction Studies

Clinical Studies

Strong CYP3A Inhibitors: Imlunestrant AUC increased 2.1-fold and C_{max} increased 1.9-fold following concomitant use of itraconazole (strong CYP3A inhibitor) for multiple days.

Strong CYP3A Inducers: Imlunestrant AUC decreased by 42% and C_{max} decreased by 29% following concomitant use of carbamazepine (strong CYP3A inducer) for multiple days.

P-gp Substrates: Digoxin (P-gp substrate) AUC increased 1.4-fold and C_{max} increased 1.6-fold following concomitant use of imlunestrant.

BCRP Substrates: Rosuvastatin (BCRP substrate) AUC increased 1.5-fold and C_{max} increased 1.6-fold following concomitant use with imlunestrant.

Other Drugs: No clinically significant differences in the pharmacokinetics of imlunestrant were observed when used concomitantly with omeprazole (gastric acid-reducing agent) or quinidine (P-gp inhibitor).

No clinically significant differences in the pharmacokinetics of midazolam (CYP3A substrate), repaglinide (CYP2C8 substrate), omeprazole (CYP2C19 substrate), or dextromethorphan (CYP2D6 substrate) were observed when used concomitantly with imlunestrant.

In Vitro Studies

CYP Enzymes: Imlunestrant is an inhibitor of CYP2B6 and CYP2C9 but is not an inhibitor of CYP1A2. Imlunestrant is not an inducer of CYP1A2, CYP2B6, or CYP2C9.

Transporter Systems: Imlunestrant is not a substrate of BCRP, OCT1, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with imlunestrant.

Mutagenesis

Imlunestrant was not mutagenic in the bacterial reverse mutation (Ames) assay. Imlunestrant was clastogenic in an in vitro human lymphocyte micronucleus assay. Imlunestrant was not genotoxic in an in vivo rat bone marrow micronucleus test and did not induce DNA breaks in the liver and duodenum comet assays.

Impairment of Fertility

Fertility studies with imlunestrant in animals have not been conducted. In repeat-dose toxicity studies up to 6 months in rats and 3 months in cynomolgus monkeys, oral administration of imlunestrant resulted in follicular cysts in the ovary and atrophy in the vagina, cervix, and uterus at doses ≥ 10 mg/kg/day in rats (≥ 4 times the human AUC at the recommended dose) and ≥ 15 mg/kg/day in cynomolgus monkeys (≥ 1 times the human AUC at the recommended dose). Decreased sperm and cellular debris in the epididymis and spermatid retention in the testis were observed in male rats at ≥ 10 mg/kg/day. The effects of imlunestrant on male and female reproductive organs were reversible in rats following a 3-month recovery period. Reversibility was not assessed in cynomolgus monkeys.

13.2 Animal Toxicology and/or Pharmacology

In a 6-month repeat-dose toxicity study, oral administration of imlunestrant to rats resulted in epithelial hyperplasia in the urinary bladder, granulosa cell hyperplasia in the ovary, and hyperplasia in the mammary gland at doses ≥ 10 mg/kg/day (≥ 4 times the human AUC at the recommended dose). These effects, except urinary bladder effects, were reversible after a 3-month recovery period.

14 CLINICAL STUDIES

The efficacy of INLURIYO was evaluated in EMBER-3 (NCT04975308), a randomized, open-label, active-controlled, multicenter trial that enrolled 874 adult patients with ER+, HER2- locally advanced or metastatic breast cancer, who were previously treated with an aromatase inhibitor either alone or in combination with a CDK4/6 inhibitor. Patients were excluded if they were eligible to receive a PARP inhibitor. Patients were required to have progressed:

- Within 12 months of completing neoadjuvant or adjuvant aromatase inhibitor therapy with no systemic treatment for recurrent disease or
- Greater than 12 months after neoadjuvant or adjuvant endocrine therapy or de novo metastatic disease and had progressed on only one line of aromatase inhibitor therapy.

Patients were randomized 1:1:1 to INLURIYO 400 mg orally once daily; or investigator's choice of endocrine therapy [fulvestrant 500 mg IM on days 1, 15, 29, and once monthly thereafter (n=111) or exemestane 25 mg orally once daily (n=6)]; or an additional investigational combination regimen. 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). *ESR1m* status was determined by blood circulating tumor deoxyribonucleic acid (ctDNA) analysis using the Guardant360 CDx assay and was limited to specific *ESR1* mutations in the ligand binding domain. Patients were treated until disease progression or unacceptable toxicity.

The major efficacy outcome was investigator assessed progression-free survival (PFS) according to RECIST v1.1. Other efficacy measures included overall survival (OS), blinded independent review committee (BIRC)-assessed PFS, and objective response rate (ORR).

Among the patients on the INLURIYO arm or investigator's choice of endocrine therapy who were positive for *ESR1m* (N=256), the median age was 61 years (range: 28-85 years); all patients were female, of which 11% were pre/perimenopausal; 61% were White, 26% Asian, 4% Black, 4% were American Indian or Alaskan Native, 4.7% missing, 0.8% multiple, 19% were Hispanic/Latino; and baseline ECOG performance status was 0 (63%) or 1 (37%). Most patients had visceral metastasis (59%) at baseline. Of the patients enrolled, 21% had received no endocrine therapy and 79% had received one line of endocrine therapy in the advanced or metastatic setting. Overall, 70% of patients were treated with a prior CDK4/6i, 2.3% treated in the adjuvant setting and 67% treated in the advanced or metastatic setting.

The efficacy results from these patients are summarized in Table 5 and Figure 1. There was a statistically significant difference in investigator-assessed PFS in the *ESR1m* population for INLURIYO compared to investigator's choice of endocrine therapy (fulvestrant or exemestane). PFS assessment based on a BIRC was consistent with the investigator assessment. At the time of PFS analysis, overall survival data was immature with 31% of deaths in the *ESR1m* population.

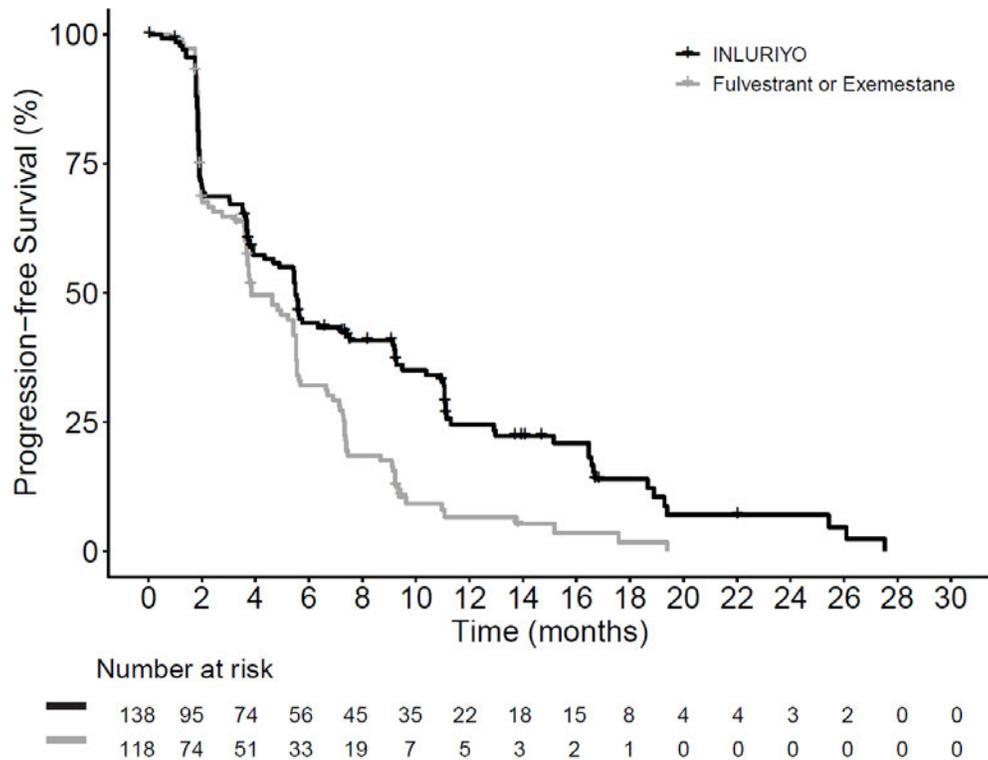
Table 5: Efficacy Results for Patients with *ESR1m* in EMBER-3

| | INLURIYO N=138 | Fulvestrant or Exemestane N=118 |
|---|---------------------------|--|
| Progression-free Survival (PFS)^{a, b} | | |
| Number of PFS Events, n (%) | 109 (79) | 102 (86) |
| Median in months (95% CI) | 5.5 (3.9, 7.4) | 3.8 (3.7, 5.5) |
| Hazard Ratio (95% CI) ^c | 0.62 (0.46, 0.82) | |
| p-value ^d | 0.0008 | |
| Objective Response Rate^b | | |
| Patients with Measurable Disease | 112 | 91 |
| ORR (95% CI) | 14.3 (7.8, 20.8) | 7.7 (2.2, 13.2) |
| Complete response rate, % | 0.9 | 0 |
| Partial response rate, % | 13.4 | 7.7 |

^a Investigator Assessed

- ^b per RECIST v1.1
- ^c Based on the stratified Cox proportional hazard model
- ^d Two-sided p-value based on stratified log-rank test (compared to a significance level of 0.04)

Figure 1: Kaplan-Meier Plot of Investigator-Assessed PFS for Patients with *ESR1m*, Treated with INLURIYO or Fulvestrant/Exemestane in EMBER-3



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

INLURIYO 200 mg tablets are white capsule-shaped tablets with “LILLY” on one side and “1717” and an elongated 4-point starburst on the other side.

INLURIYO 200 mg tablets are supplied in either a 28-count or 56-count bottle configuration.

- 28-count: NDC 0002-1717-28
- 56-count: NDC 0002-1717-56

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). Excursions between 15°C to 30°C (59°F to 86°F) are permitted [see *USP Controlled Room Temperature*].

Disposal

Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Dyslipidemia

Advise patients that hypercholesterolemia and hypertriglyceridemia may occur while taking INLURIYO. Inform patients that lipid profile monitoring will be performed prior to starting and periodically while taking INLURIYO [see *Adverse Reactions (6.1)*].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with INLURIYO and for 1 week after the last dose [see *Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with INLURIYO and for 1 week after the last dose [see *Use in Specific Populations (8.2)*].

Infertility

Advise males and females of reproductive potential that INLURIYO may impair fertility [see *Use in Specific Populations (8.3)*].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over the counter drugs, and herbal products [see *Drug Interactions (7.1, 7.2)*].

Dosing Instructions

Instruct patients to take INLURIYO at approximately the same time each day and to swallow the tablet(s) whole. Tablets should not be chewed, crushed, or split prior to swallowing [see *Dosage and Administration (2.1)*].

Advise patients to take INLURIYO without food, either 2 hours before food or 1 hour after food [see *Dosage and Administration (2.1)*].

Instruct patient that if a dose of INLURIYO is missed by more than 6 hours or vomiting occurs, skip the dose and take the next dose the following day at its regularly scheduled time [see *Dosage and Administration (2.1)*].

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INL-0001-USPI-202509

PATIENT INFORMATION
INLURIYO™ (en-loo-ree-yoh)
imlunestrant
tablets

What is INLURIYO?

INLURIYO is a prescription medicine used to treat adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *estrogen receptor-1 (ESR1)*-mutated advanced breast cancer or breast cancer that has spread to other parts of the body (metastatic), and whose disease has progressed after at least 1 line of endocrine therapy.

Your healthcare provider will perform a test to make sure that INLURIYO is right for you.

It is not known if INLURIYO is safe and effective in children.

Before taking INLURIYO, tell your healthcare provider about all of your medical conditions including if you:

- have liver problems.
- are pregnant or plan to become pregnant. INLURIYO can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will do a pregnancy test before you start treatment with INLURIYO.
- Use effective birth control (contraception) during treatment with INLURIYO and for 1 week after the last dose.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with INLURIYO.

Males with female partners who are able to become pregnant:

- Use effective birth control (contraception) during treatment with INLURIYO and for 1 week after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if INLURIYO passes into breastmilk. Do not breastfeed during treatment with INLURIYO and for 1 week after the last dose.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. INLURIYO and other medicines may affect each other causing side effects. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take INLURIYO?

- Take INLURIYO exactly as your healthcare provider tells you.
- Do not stop taking INLURIYO or change the dose unless your healthcare provider tells you to.
- Take INLURIYO 1 time a day at about the same time each day.
- Take INLURIYO on an empty stomach, at least 2 hours before food or 1 hour after food.
 - Swallow INLURIYO tablets whole. Do not chew, crush, or split the tablets.
- If you miss a dose of INLURIYO by 6 or more hours or vomit after taking INLURIYO, do not take another dose on that day. Take your next dose the following day at your regularly scheduled time.

What are the possible side effects of INLURIYO?

The most common side effects of INLURIYO include:

- | | |
|-------------------------------------|---------------------------------|
| • decreased hemoglobin (anemia) | • nausea |
| • muscle and joint pain | • decreased platelet counts |
| • decreased white blood cell counts | • constipation |
| • increased liver function tests | • stomach-area (abdominal) pain |
| • decreased calcium blood levels | |

- tiredness
- diarrhea
- increased triglyceride and cholesterol blood levels.
Your healthcare provider will check your blood levels before and during treatment with INLURIYO.

Your healthcare provider may change your dose, temporarily stop, or completely stop treatment with INLURIYO if you develop certain side effects.

INLURIYO may affect fertility in males and in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of INLURIYO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store INLURIYO?

- Store INLURIYO at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away (dispose of) unused INLURIYO by a medicine take-back program if available. If no take-back program is available, visit www.fda.gov/drugdisposal for instructions on how to throw away medicines in the household trash.
- **Do not** flush INLURIYO down the toilet.

Keep INLURIYO and all medicines out of the reach of children.

General information about the safe and effective use of INLURIYO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INLURIYO for a condition for which it was not prescribed. Do not give INLURIYO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about INLURIYO.

What are the ingredients in INLURIYO?

Active ingredient: imlunestrant

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose. The tablet coating contains polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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For more information, go to www.INLURIYO.com or call 1-800-545-5979

NDC 0002-1717-28
Rx only

Inluriyo™
 (imlunestrant) tablets
200 mg

Do not use if inner seal is missing or broken.
 Each tablet contains: imlunestrant 200 mg (equivalent to 265.66 mg of imlunestrant tosylate).
 Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
 Keep out of reach of children.
 Recommended dosage:
 See Prescribing Information.

28 tablets *Lilly* (01)00300021717285

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 Product of Ireland
 NLO34EMAM00
 GTIN: 00300021717285

LOT: XXXXXXXX
 EXP: YYYY-MM-DD
 SN: XXXXXXXXXXXX

FPO



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NDC 0002-1717-56
Rx only

Inluriyo™
 (imlunestrant) tablets
200 mg

56 tablets *Lilly*

Do not use if inner seal is missing or broken.
 Each tablet contains: imlunestrant 200 mg (equivalent to 265.66 mg of imlunestrant tosylate).
 Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
 Keep out of reach of children.
 Recommended dosage:
 See Prescribing Information.

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 Product of Ireland
 NLO35EMAM00
 GTIN: 00300021717568

LOT: XXXXXXXX
 EXP: YYYY-MM-DD
 SN: XXXXXXXXXXXX

FPO

(01)00300021717568



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