HIGHLIGHTS OF PRESCRIBING INFORMATION

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

WILSERDLY™ (giredestrant) capsules, for oral use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------

WILSERDLY is an estrogen receptor antagonist indicated in combination with everolimus for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated locally advanced or metastatic breast cancer, as detected by an FDA-authorized test, whose disease has recurred during or after completion of endocrine-based adjuvant therapy, or has progressed on at least one endocrine-based regimen in the metastatic setting. (1, 14)

----------DOSAGE AND ADMINISTRATION----------

WILSERDLY is taken in combination with everolimus.

- Select patients for treatment based on the presence of *ESR1* mutations. (2.1)
- The recommended dosage of WILSERDLY is 30 mg orally once daily, with or without food. (2.2)
- Dosage interruption or discontinuation may be required due to adverse reactions. Dosage reduction is not recommended. (2.3)
- See full Prescribing Information for dosage modifications of WILSERDLY due to adverse reactions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 30 mg giredestrant (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Bradycardia: WILSERDLY can cause a decrease in heart rate. Monitor heart rate more frequently in patients who already have bradycardia or who are taking other medications known to slow the heart rate. Withhold or permanently discontinue WILSERDLY based on severity. (2.3, 5.1)
- Embryo-fetal toxicity: WILSERDLY can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common (≥20%) adverse reactions and laboratory abnormalities with WILSERDLY in combination with everolimus were: decreased hemoglobin, decreased lymphocytes, decreased white blood cells, increased AST, increased ALT, stomatitis, decreased neutrophils, decreased platelets, decreased calcium, decreased potassium, rash, increased creatinine, fatigue, diarrhea, decreased sodium, musculoskeletal pain, pneumonitis, and nausea. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088, or www.fda.gov/medwatch**.**

---------- DRUG INTERACTIONS ----------

- Strong CYP3A Inhibitors: Avoid concomitant use. (7.1)
- Strong CYP3A Inducers: Avoid concomitant use. (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: 11/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WILSERDLY, in combination with everolimus, is indicated for the treatment of adults with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), *ESR1*-mutated locally advanced or metastatic breast cancer, as detected by an FDA-authorized test, whose disease has recurred during or after completion of endocrine-based adjuvant therapy, or has progressed on at least one endocrine-based regimen in the metastatic setting.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of ER-positive, HER2-negative locally advanced or metastatic breast cancer with WILSERDLY, based on the presence of *ESR1* mutation(s) in a plasma specimen using an FDA-authorized test *[see Indications and Usage (1) and Clinical Studies (14)]*.

Information on FDA-authorized 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 WILSERDLY is 30 mg taken orally once daily with or without food. Swallow WILSERDLY capsules whole. Do not open, chew, or crush the capsules.

Continue until disease progression or unacceptable toxicity.

For pre- or peri-menopausal women, and men, administer a gonadotropin-releasing hormone (GnRH) agonist in accordance with current clinical practice standards.

Take WILSERDLY at approximately the same time each day. If a dose is missed, take the missed dose as soon as possible on the same day and take the next dose at the regularly scheduled time.

If a dose is vomited, do not take an additional dose and take the next dose at the regularly scheduled time.

Administer WILSERDLY in combination with everolimus. Refer to the full Prescribing Information for everolimus for dosage information.

2.3 Dosage Modification for Adverse Reactions

The recommended dosage modifications for adverse reactions are listed in Table 1. Management of some adverse reactions may require dosage interruption and/or discontinuation. Dosage reductions are not recommended.

Table 1: WILSERDLY Recommended Dosage Modifications for Adverse Reactions

Adverse Reactions	Severity*	Dosage Modifications
Bradycardia	Grade 2 (symptomatic)	Withhold WILSERDLY. Evaluate concomitant drug products known to cause bradycardia, including anti-hypertensive medications, and reduce the dosage or discontinue the concomitant medication, if appropriate. Resume WILSERDLY after recovery to Grade ≤ 1 (asymptomatic bradycardia) and heart rate is > 50 bpm. For recurrent Grade 2 bradycardia, permanently discontinue WILSERDLY.
	Grade ≥ 3 (intervention required; life-threatening consequences, urgent intervention indicated)	Permanently discontinue WILSERDLY if no contributing concomitant medicinal product is identified. If a contributing concomitant medication is identified and modified, withhold WILSERDLY until recovery to Grade ≤ 1.
Other Adverse Reactions	Grade 3	Temporarily withhold WILSERDLY, until recovery to Grade ≤ 1.
	Grade 4	Permanently discontinue WILSERDLY.

*Based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0

3 DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg giredestrant in capsules, with a pink cap and brown body, with “GIR 30” printed in white ink on the capsule body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Bradycardia

WILSERDLY can cause a decrease in heart rate.

In the evERA Breast Cancer study, bradycardia occurred in 3.8% of patients who received WILSERDLY in combination with everolimus; all were asymptomatic (Grade 1). The mean heart rate decrease from baseline was approximately 7 beats per minute and plateaued after 2 weeks of treatment.

Monitor heart rate more frequently in patients with pre-existing bradycardia and in those receiving concomitant medications known to cause bradycardia, such as beta-blockers, calcium channel blockers, alpha agonists, and digoxin. If patients experience symptomatic bradycardia, withhold WILSERDLY and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified, reduce the dosage or discontinue the concomitant medication, if appropriate. Resume WILSERDLY following resolution of symptomatic bradycardia. Permanently discontinue WILSERDLY for life-threatening bradycardia if no contributing concomitant medication is identified *[see Dosage and Administration (2.3)]*.

No effects on exercise tolerance or blood pressure were detected in a dedicated cardiac effects study (N=20).

5.2 Embryo-fetal Toxicity

Based on findings in animals and its mechanism of action, WILSERDLY can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, daily oral administration of giredestrant to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities at maternal exposures equivalent to the human exposure at the recommended dose based on AUC.

Advise pregnant patients and females of reproductive potential of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with WILSERDLY and for 2 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during therapy with WILSERDLY and for 2 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

WILSERDLY is used in combination with everolimus. Refer to the full Prescribing Information of everolimus for pregnancy and contraception information.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Bradycardia *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials 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.

<u>evERA Breast Cancer</u>

The safety of WILSERDLY was evaluated in 368 patients with ER+, HER2- locally advanced or metastatic breast cancer following endocrine therapy in combination with a CDK4/6 inhibitor in the evERA Breast Cancer study *[see Clinical Studies (14)]*. Patients received WILSERDLY 30 mg orally once daily and everolimus 10 mg orally once daily (N=182) or physician's choice of endocrine therapy (exemestane, fulvestrant, or tamoxifen) and everolimus 10 mg orally once daily (N=186). Among patients who received WILSERDLY and everolimus, the median duration of exposure to WILSERDLY was 7.1 months (range: 0.5 to 28.8 months).

Serious adverse reactions occurred in 29% of patients who received WILSERDLY in combination with everolimus. Serious adverse reactions that occurred in >2% of patients included pneumonia (5%) and pneumonitis (4.9%).

Fatal adverse reactions occurred in 2.7% of patients who received WILSERDLY in combination with everolimus, including pneumonia (1.6%), intestinal perforation due to strangulated hernia (0.5%), and unknown cause (0.5%).

Permanent discontinuation of WILSERDLY due to an adverse reaction occurred in 8% of patients who received WILSERDLY in combination with everolimus. Adverse reactions which resulted in permanent discontinuation of WILSERDLY in >1% of patients included pneumonia and renal failure.

Dosage interruption of WILSERDLY due to an adverse reaction occurred in 37% of patients who received WILSERDLY in combination with everolimus. Adverse reactions which resulted in dosage interruption of WILSERDLY in >2% of patients included pneumonitis, COVID-19, increased AST, pneumonia, diarrhea, rash, and stomatitis.

The most common (≥20%) adverse reactions including laboratory abnormalities with WILSERDLY in combination with everolimus were decreased hemoglobin, decreased lymphocytes, decreased white blood cells, increased AST, increased ALT, stomatitis, decreased neutrophils, decreased platelets, decreased calcium, decreased potassium, rash, increased creatinine, fatigue, diarrhea, decreased sodium, musculoskeletal pain, pneumonitis, and nausea.

Adverse reactions and laboratory abnormalities in evERA Breast Cancer are summarized in Table 2 and Table 3, respectively.

Table 2: Adverse Reactions (≥10%) in Patients who Received WILSERDLY in Combination with Everolimus in the evERA Breast Cancer Study

Adverse Reactions	**WILSERDLY + Everolimus N = 182**		**Exemestane, fulvestrant, or tamoxifen + Everolimus N = 186**	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Stomatitis[1]	52	2.7	54	3.2
Diarrhea	27	0	23	1
Nausea	22	0.5	17	1
Vomiting	12	0	13	0.5
Skin and subcutaneous tissue disorders				
Rash[2]	33	2.2	30	0.5
General disorders and administration site conditions				
Fatigue[3]	28	1	27	2
Edema[4]	18	0	15	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[5]	26	1	28	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[6]	23	3.8	16	2.7
Cough[7]	15	0.5	11	0
Metabolism and nutrition disorders				
Decreased appetite	19	0	14	1.6
Nervous system disorders				
Headache	13	1	16	0

Dysgeusia[8]	11	0	10	0.5

Grading according to NCI CTCAE version 5.0.
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
[1]includes stomatitis, mouth ulceration, aphthous ulcer, pharyngeal inflammation, mucosal inflammation, cheilitis, glossitis
[2]includes rash, rash maculo-papular, eczema, dermatitis acneiform, dermatitis, rash pruritic, rash pustular, palmar-plantar erythrodysaesthesia syndrome, drug eruption, eyelid rash, rash erythematous, and rash papular
[3]includes fatigue and asthenia
[4]includes peripheral edema, face edema, edema, swelling, periorbital edema, localized edema, and eyelid edema
[5]includes back pain, musculoskeletal pain, myalgia, pain in extremity, arthralgia, musculoskeletal chest pain, muscle discomfort, limb discomfort, and musculoskeletal discomfort
[6]includes pneumonitis and interstitial lung disease
[7]includes cough and productive cough
[8]includes dysgeusia and ageusia

Clinically relevant adverse reactions occurring in <10% of patients who received WILSERDLY in combination with everolimus included urinary tract infection, hot flush, bradycardia, dizziness, and renal failure.

Table 3: Select Laboratory Abnormalities (≥10%) that Worsened from Baseline in Patients who Received WILSERDLY in Combination with Everolimus in the evERA Breast Cancer Study

Parameter	WILSERDLY + Everolimus[a] N=182		Exemestane, fulvestrant, or tamoxifen + Everolimus[b] N=186	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Hemoglobin decreased	77	7[c]	75	11[c]
Lymphocytes decreased	68	16	68	15
WBC* decreased	65	2.2[c]	66	3.2
Neutrophils decreased	50	4.4	47	3.8
Platelets decreased	50	2.2	47	2.7
Chemistry				
Aspartate aminotransferase increased	62	6[c]	64	3.8[c]
Alanine aminotransferase increased	54	3.9[c]	57	2.7[c]
Calcium decreased	44	2.2	38	1.6
Potassium decreased	36	7	33	3.2
Creatinine increased	30	1.7	27	1.6
Sodium decreased	27	0.6	22	2.2

* White blood cell count

[a] The denominator used to calculate the rate varied from 181 to 182 based on the number of patients with a baseline value and at least one post-treatment value

[b] The denominator used to calculate the rate varied from 185 to 186 based on the number of patients with a baseline value and at least one post-treatment value

[c] No grade 4 laboratory abnormalities

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on WILSERDLY

Table 4 describes drug interactions where concomitant use of another drug affects WILSERDLY.

Table 4: Drug Interactions that Affect WILSERDLY

Strong CYP3A Inhibitors	
Prevention or Management	• Avoid concomitant use of WILSERDLY with strong CYP3A inhibitors.
Mechanism and Clinical Effect	• Giredestrant is a CYP3A substrate. Concomitant use with strong CYP3A inhibitors increases giredestrant plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of WILSERDLY-associated adverse reactions.
Strong CYP3A Inducers	
Prevention or Management	• Avoid concomitant use of WILSERDLY with strong CYP3A inducers.
Mechanism and Clinical Effect	• Giredestrant is a CYP3A substrate. Concomitant use with strong CYP3A inducers decreases giredestrant plasma concentrations *[see Clinical Pharmacology (12.3)],* which may decrease the effectiveness of WILSERDLY.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

WILSERDLY is used in combination with everolimus. Refer to the full Prescribing Information of everolimus for pregnancy information.

Based on findings in animals and its mechanism of action, WILSERDLY can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data on WILSERDLY use in pregnant women to inform the drug-associated risk. In an animal reproduction study, daily oral administration of giredestrant to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities at maternal exposure equivalent to 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.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, giredestrant was administered orally to pregnant rats during the period of organogenesis from gestation days 7 to 17 at doses of 3 and 10 mg/kg that resulted in polyhydramnios and uterine rupture, embryo-fetal mortality (post-implantation loss, decreased number of live fetuses), and malformations (including domed heads, meningocele, maxillary micrognathia) at ≥3 mg/kg (equivalent to the human exposure at the recommended dose based on AUC).

8.2 Lactation

Risk Summary

WILSERDLY is used in combination with everolimus. Refer to the full Prescribing Information of everolimus for lactation information.

There are no data on the presence of giredestrant 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 not to breastfeed during treatment with WILSERDLY and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

WILSERDLY is used in combination with everolimus; refer to the everolimus Prescribing Information for contraception and infertility information. Advise patients to use effective contraception following the last dose based on the longest duration recommended in the respective Prescribing Information.

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

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating WILSERDLY treatment.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WILSERDLY and for 2 weeks after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WILSERDLY and for 2 weeks after the last dose.

Infertility

Based on findings in animals, WILSERDLY 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 WILSERDLY have not been established in pediatric patients.

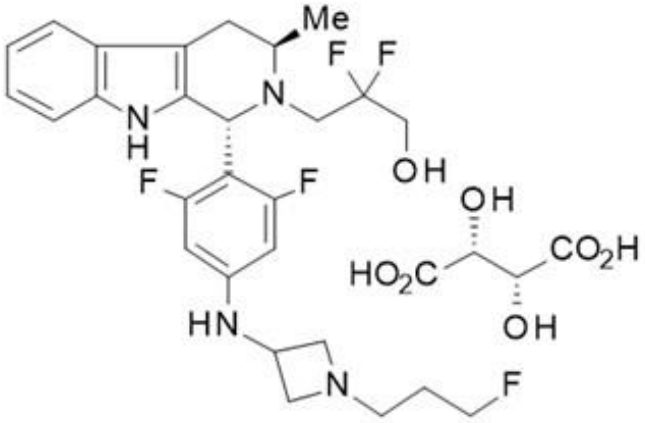
8.5 Geriatric Use

In evERA Breast Cancer, 41% of patients who received WILSERDLY were ≥ 65 years of age, and 13% were ≥ 75 years of age. Compared to those younger than 65 years, adults ≥ 75 years had higher incidences of SAEs (38% vs 26%), AEs leading to any treatment discontinuation (38% vs 13%), and dosage interruptions of any treatment due to AEs (63% vs 55%). Patients aged 65-74 had similar incidences of SAEs, AEs leading to treatment discontinuation, and dosage interruptions to those < 65 years.

Clinical studies of WILSERDLY did not include sufficient numbers of patients ≥ 65 years of age to determine whether efficacy differs compared to that of younger patients.

11 DESCRIPTION

WILSERDLY (giredestrant) is an estrogen receptor antagonist. The molecular formula for giredestrant tartrate is $C_{27}H_{31}F_5N_4O \bullet C_4H_6O_6$ and the molecular weight is 522.55 g/mol (free base) and 672.64 g/mol (tartrate salt). The chemical name of giredestrant tartrate is 3-[(1*R*,3*R*)-1-(2,6-difluoro-4-{[1-(3-fluoropropyl)azetidin-3-yl]amino}phenyl)-3-methyl-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl]-2,2-difluoropropan-1-ol (2*R*,3*R*)-2,3-dihydroxybutanedioic acid. The chemical structure of giredestrant tartrate is shown below:



WILSERDLY is supplied as hard capsules for oral administration containing 30 mg of giredestrant (equivalent to 38.62 mg giredestrant tartrate), and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The capsule shell contains black iron oxide, hypromellose, red iron oxide, titanium dioxide, and yellow iron oxide. The printing ink contains propylene glycol, shellac, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Giredestrant is an estrogen receptor (ER) antagonist that binds to the ligand binding domain of ERα, antagonizes the activity of ERα encoded by wild type and mutated *ESR1*, and induces degradation of ERα protein without agonizing ERα. Giredestrant inhibited the proliferation of ER-positive breast cancer cells *in vitro* and *in vivo*, including in models that harbor *ESR1* mutations. In vitro, the combination of giredestrant with everolimus led to greater antiproliferative effects on ER-positive breast cancer cells compared to giredestrant alone.

12.2 Pharmacodynamics

Exposure-Response Relationship

Giredestrant exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At 2.4 times the mean maximum giredestrant concentration observed at the recommended dosage, a mean increase in the QTc interval > 20 ms is unlikely.

12.3 Pharmacokinetics

Giredestrant pharmacokinetics were observed at steady state in patients at the approved recommended dosage and are presented as mean (CV%), unless otherwise specified.

Giredestrant maximum concentration (C_{max}) is 266 (50%) ng/mL and systemic exposure (AUC) is 4,320 (59%) ng*h/mL. Giredestrant steady-state C_{max} increased 1.8-fold and AUC increased 1.9-fold when administered in combination with everolimus. Giredestrant C_{max} and AUC increase in a dose-proportional manner over the dosage range of 10 mg to 250 mg (0.33 to 8.3 times the approved recommended dosage) once daily. Giredestrant steady-state is reached by Day 8. Giredestrant accumulation is 1.8-fold for C_{max} and 2.4-fold for AUC.

Absorption

Giredestrant median (min, max) time to maximum plasma concentration (T_{max}) is 3 (1.5, 3.8) hours. Giredestrant absolute oral bioavailability is 58%.

Effect of Food

No clinically significant differences in giredestrant pharmacokinetics were observed following administration of a high-fat meal (1000 calories, 50% fat) in healthy subjects.

Distribution

Giredestrant apparent (oral) volume of distribution is 365 (32%) L. Plasma protein binding of giredestrant is >98% and is not concentration dependent. The blood-to-plasma concentration ratio is 0.8.

Elimination

Giredestrant half-life is 43 (15%) hours with an apparent clearance of 5.9 (30%) L/hr.

Metabolism

Giredestrant is primarily metabolized by CYP3A (major) and glucuronidation (minor).

Excretion

After a single oral 30 mg dose of radiolabeled giredestrant to healthy subjects, 68% of the dose was recovered in feces (20% unchanged) and 9% in urine (1.9% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of giredestrant were observed based on age (27 to 87 years), body weight (38 to 165 kg), race (White [63%], Asian [32%], Black or African American [2%]), creatinine clearance (CLcr) 30 to < 90 mL/min (calculated using the Cockcroft-Gault equation), and hepatic impairment (Child-Pugh Class A, B, and C). The effect of CLcr < 30 mL/min or end-stage renal disease (CLcr < 15 mL/min) on the pharmacokinetics of giredestrant is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Everolimus: Giredestrant steady state C_{max} increased 1.8-fold and steady state AUC increased 1.9-fold following concomitant use with everolimus 10 mg once daily for 28 days.

No clinically significant differences in the pharmacokinetics of everolimus were observed following concomitant use with giredestrant.

Strong and Moderate CYP3A Inhibitors: Giredestrant C_{max} increased 1.4-fold and AUC increased 4-fold following concomitant use with itraconazole (strong CYP3A inhibitor) 200 mg twice daily on day 1, followed by 200 mg once daily for 13 days.

Giredestrant AUC is predicted to increase 1.9 to 2.5-fold following concomitant use of multiple doses of erythromycin, fluconazole, or diltiazem (moderate CYP3A inhibitors).

Strong CYP3A Inducers: Giredestrant C_{max} decreased to 50% and AUC decreased to 24% following concomitant use with carbamazepine (strong CYP3A inducer) 100 mg twice daily for 3 days, followed by 200 mg twice daily for 3 days, 300 mg twice daily for 13 days, 200 mg twice daily for 1 day, and then 100 mg twice daily for 1 day.

Other Drugs: No clinically significant differences in the pharmacokinetics of the following drugs are predicted when used concomitantly with WILSERDLY: oral midazolam (CYP3A substrate).

In vitro Studies

CYP450 Enzymes: Giredestrant inhibits CYP2B6, CYP2C8, and CYP2C9, but does not inhibit CYP1A2, CYP2C19, or CYP2D6. Giredestrant induces CYP2B6 but does not induce CYP1A2.

Transporter Systems: Giredestrant is a substrate of P-gp, but not a substrate of BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE-2K, OAT1, or OAT3. Giredestrant inhibits P-gp, BCRP, OATP1B1, OCT1, and MATE1 but does not inhibit OATP1B3, OCT2, MATE-2K, OAT1, or OAT3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 6-month rasH2 transgenic mouse study, daily oral administration of giredestrant led to an increased incidence of benign ovarian tumors (luteoma, granulosa cell tumor, and/or mixed sex chord stromal tumor) in females administered ≥ 10 mg/kg. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Mutagenesis

Giredestrant was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay. Giredestrant was not clastogenic in an *in vitro* human lymphocyte micronucleus assay or in an *in vivo* rat bone marrow micronucleus test.

Impairment of Fertility

Fertility studies with giredestrant in animals have not been conducted. In repeat-dose toxicity studies up to 6 months in female rats and monkeys, daily oral administration of giredestrant resulted in disrupted estrous cycle, ovarian follicular cysts, atrophy in vagina, cervix, and uterus, and epithelial mucification in vagina and cervix at doses ≥ 3 mg/kg in rats and ≥ 7 mg/kg in monkeys (equivalent to the human AUC at the recommended dose). In a 3-month repeat-dose toxicity study in male rats, daily oral administration of giredestrant resulted in degeneration/atrophy in the seminiferous tubule of testes at 30 mg/kg (6 times the human AUC at the recommended dose). Findings were reversible following a 16-week recovery period.

13.2 Animal Toxicology and/or Pharmacology

In repeat-dose rat studies, daily oral administration of giredestrant for 3 and 6 months to male and female rats, respectively, induced chronic nephropathy at 30 mg/kg (≥6 times the human AUC at the recommended dose), which correlated with clinical pathology findings consistent with renal injury. Chronic nephropathy did not recover following a 16-week recovery period.

14 CLINICAL STUDIES

Locally Advanced or Metastatic Breast Cancer

The efficacy of WILSERDLY in combination with everolimus was evaluated in evERA Breast Cancer (NCT05306340), a randomized, open-label multicenter trial in 373 adults with ER+, HER2- locally advanced or metastatic breast cancer including 207 patients whose tumors had *ESR1* mutations. Patients were required to have:

- Disease progression after ≥ 6 months on endocrine therapy in combination with a CDK4/6 inhibitor in the locally advanced or metastatic setting or
- Recurrence on, or within 12 months of completing, adjuvant endocrine therapy, including ≥ 6 months in combination with a CDK4/6 inhibitor.

Patients were randomized 1:1 to receive WILSERDLY 30 mg once daily (N=183) or physician's choice of endocrine therapy (N=190), which included exemestane, fulvestrant, or tamoxifen. Patients in both arms also received everolimus 10 mg once daily. Pre-/peri-menopausal female patients received an GnRH agonist for ovarian function suppression. Male patients also received an GnRH agonist, except in the case of bilateral orchiectomy.

Randomization was stratified by *ESR1* mutation status (detected vs not detected), prior treatment with fulvestrant (yes vs no), and visceral disease (liver and/or lung involvement, yes vs no). *ESR1* mutation status was assessed centrally in plasma-derived circulating tumor DNA (ctDNA) using the FoundationOne® Liquid CDx assay and was limited to specific *ESR1* mutations in the ligand binding domain. Patients were treated until disease progression or unacceptable toxicity.

Among the patients whose tumors had an *ESR1* mutation (n=207), the median age was 59 years (range: 32-83); 98.6% were female; 66% were White, 26% Asian, 4.3% Black, 25% were Hispanic/Latino; baseline ECOG performance status was 0 (69%) or 1 (31%). Of the 204 female patients, 14% were pre-/peri-menopausal. Most patients (73%) had visceral disease; 75% had received 1 prior line of endocrine therapy, and 23% had received 2 prior lines of endocrine therapy in the advanced or metastatic setting. All patients had received prior treatment with a CDK4/6 inhibitor, and 36% had received prior treatment with fulvestrant. None had received prior chemotherapy or antibody-drug conjugates for metastatic breast cancer.

The primary efficacy outcome measure of the study was progression-free survival (PFS) by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy endpoints included overall survival (OS) and objective response rate (ORR).

A statistically significant difference in PFS was observed for WILSERDLY compared with physician's choice of endocrine therapy, both given in combination with everolimus, in patients whose tumors had an *ESR1* mutation. At the time of PFS analysis, overall survival data were immature with 32% of deaths in the *ESR1*-mutated population. Efficacy results for the *ESR1*-mutated population are provided in Table 5 and Figure 1.

Table 5: Efficacy Results for evERA Breast Cancer (Patients with *ESR1*-Mutated Tumors)

Efficacy Endpoint	*ESR1*m subpopulation	
	WILSERDLY + everolimus N=102	**Exemestane, fulvestrant, or tamoxifen + everolimus N=105**
Progression-Free Survival[a,b]		
Patients with event, n (%)	63 (62)	89 (85)
Median in months (95% CI)	10.0 (8.1, 12.9)	5.5 (3.8, 5.6)
Hazard ratio[c] (95% CI)	0.38 (0.27, 0.54)	
p-value (2-sided)[d]	< 0.0001	
Confirmed Objective Response Rate[a,b]		
Patients with measurable disease	94	94
ORR % (95% CI)	27 (18, 37)	14 (8, 22)
Complete response rate (%)	1	0
Partial response rate (%)	26	14

CI = confidence interval

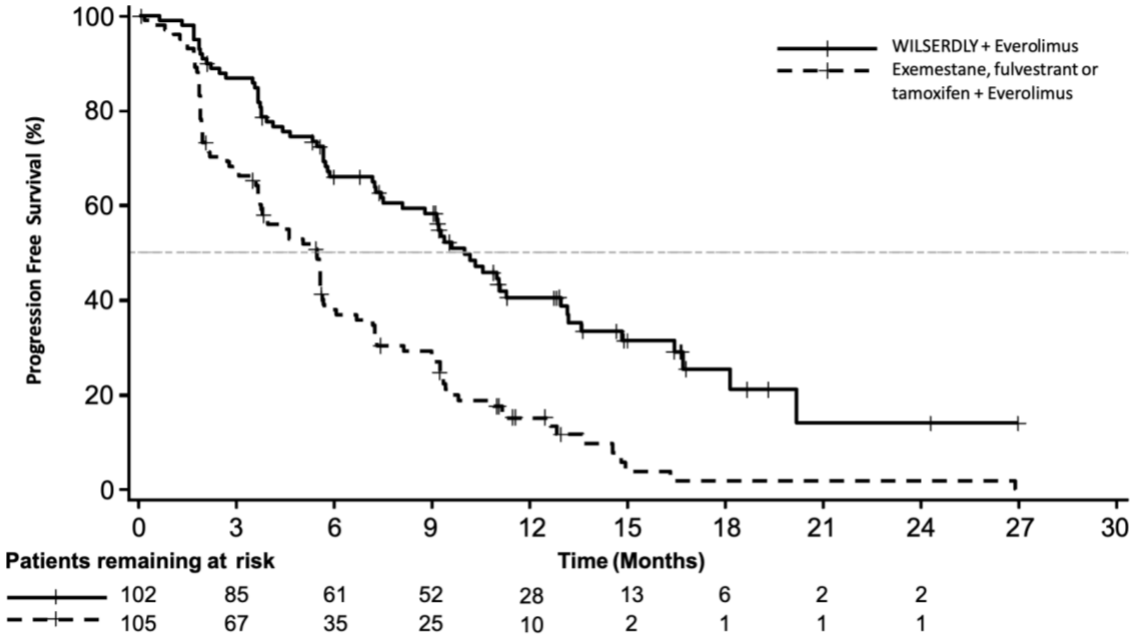
[a] Per RECIST version 1.1.

[b] Based on investigator assessment.

[c] Based on the stratified Cox proportional hazard model.

[d] Based on a stratified log-rank test.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment in evERA Breast Cancer (Patients with *ESR1*-Mutated Tumors)



16 HOW SUPPLIED/STORAGE AND HANDLING

WILSERDLY is supplied as capsules with a pink cap and brown body, containing 30 mg giredestrant, with "GIR 30" printed in white ink on the capsule body, available in:

28 capsules per bottle in a carton: NDC 50242-083-01

84 capsules per bottle in a carton: NDC 50242-083-03

Store at 20ºC to 25ºC (68ºF to 77ºF), excursions are permitted between 15ºC and 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

Store and dispense in the original bottle. Keep the bottle tightly closed to protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

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

Bradycardia

Inform patients that symptoms of bradycardia, including dizziness, tiredness, and fainting, can occur while taking WILSERDLY. Advise patients to contact their healthcare provider to report these symptoms and to inform their healthcare provider about the use of any heart or blood pressure medications or other medications that can slow the heart rate *[see Warnings and Precautions (5.1)]*.

Embryo-fetal Toxicity

Advise patients of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare providers of a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WILSERDLY and for 2 weeks after the last dose. Advise male patients with female partners of reproductive

potential to use effective contraception during treatment with WILSERDLY and for 2 weeks after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed during treatment with WILSERDLY and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that WILSERDLY 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)]*.

Dosing Instructions

Instruct patients to take WILSERDLY at approximately the same time each day and to swallow the capsule whole. Capsules should not be opened, chewed or crushed prior to swallowing *[see Dosage and Administration (2.2)]*.

Advise patients that if a dose is missed, it may be taken as soon as possible on the same day and the next dose can be taken at the regularly scheduled time *[see Dosage and Administration (2.2)]*.

If a patient vomits after taking a dose, advise the patient not to take another dose but to take the prescribed dose at the regularly scheduled time the next day *[see Dosage and Administration (2.2)]*.

Lactose

Inform patients that WILSERDLY capsules contain lactose monohydrate.

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

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PATIENT INFORMATION
WILSERDLY™ (wil-SERD-lee)
(giredestrant)
capsules, for oral use

What is WILSERDLY?

WILSERDLY is a prescription medicine used in combination with the medicine everolimus to treat adults with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer that has an estrogen receptor-1 (*ESR1)* gene mutation and has spread to nearby tissue or lymph nodes (locally advanced) or to other parts of the body (metastatic) whose cancer:

- has come back during or after finishing hormone (endocrine) treatment given after surgery (adjuvant therapy),

or

- has worsened after at least one type of endocrine treatment for metastatic cancer.

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

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

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

- have a slow heart rate (bradycardia)
- are pregnant or plan to become pregnant. WILSERDLY 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 WILSERDLY.
  - Use effective non-hormonal birth control (contraception) during treatment with WILSERDLY and for 2 weeks after the last dose of WILSERDLY. Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant during treatment with WILSERDLY or think you may be pregnant.

  Males with female partners who are able to become pregnant:
  - Use effective birth control (contraception) during treatment with WILSERDLY, and for 2 weeks after the last dose of WILSERDLY.
- are breastfeeding or plan to breastfeed. It is not known if WILSERDLY passes into your breast milk. **Do not** breastfeed during treatment with WILSERDLY and for 2 weeks after the last dose of WILSERDLY. Talk to your healthcare provider about the best way to feed your baby during this time.
- have an intolerance to some sugars found in milk and milk products. WILSERDLY capsules contain lactose monohydrate.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Taking WILSERDLY with certain other medicines may affect how WILSERDLY works and may cause side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take WILSERDLY?

- Take WILSERDLY exactly as your healthcare provider tells you to take it.
- **Do not** change your dose or stop taking WILSERDLY unless your healthcare provider tells you to.
- Your healthcare provider may temporarily or permanently stop treatment with WILSERDLY if you have side effects.
- Take WILSERDLY 1 time a day, at about the same time each day.
- Take WILSERDLY with or without food.
- Swallow WILSERDLY capsules whole. **Do not** open, chew, or crush the capsules before swallowing.
- If you miss a dose of WILSERDLY, take the missed dose as soon as possible on the same day and take the next dose at your regularly scheduled time.
- If you vomit after taking a dose of WILSERDLY, do not take an extra dose. Take your next dose at your regularly scheduled time the next day.
- Follow your healthcare providers' instructions for taking everolimus.

- For women who have not yet reached menopause or are just starting menopause, your healthcare provider may prescribe a medicine called a gonadotropin-releasing hormone (GnRH) agonist.
- For men, your healthcare provider may prescribe a gonadotropin-releasing hormone (GnRH) agonist.

What should I avoid while taking WILSERDLY?

Avoid eating grapefruit and drinking grapefruit juice during treatment with WILSERDLY. Grapefruit may increase the amount of WILSERDLY in your blood.

What are the possible side effects of WILSERDLY?

WILSERDLY can cause serious side effects, including:

- **Slow heart rate (bradycardia).** WILSERDLY can cause your heart rate to slow down. Your healthcare provider will monitor your heart rate more frequently if you have a history of a slow heart rate or take certain heart medicines. Tell your healthcare provider if you develop any signs and symptoms of a slow heart rate, including:
  - dizziness
  - lightheadedness
  - fainting
  - shortness of breath
  - chest pain
  - tiredness

The most common side effects and abnormal blood test results of WILSERDLY in combination with everolimus include:

- decreased red blood cell counts
- decreased white blood cell counts
- increased liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT])
- mouth sores (stomatitis)
- decreased platelet counts
- decreased calcium blood levels
- decreased potassium blood levels
- rash
- increased creatinine blood levels (kidney function test)
- tiredness
- decreased sodium blood levels
- diarrhea
- muscle and joint pain
- lung or breathing problems
- nausea

WILSERDLY 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 the possible side effects of WILSERDLY.

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 WILSERDLY?

- Store WILSERDLY at room temperature between 68ºF and 77ºF (20ºC and 25ºC).
- Store WILSERDLY in the original bottle.
- Keep the bottle tightly closed to protect from light and moisture.

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

General information about the safe and effective use of WILSERDLY.

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

What are the ingredients in WILSERDLY?

Active ingredient: giredestrant

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The capsule shell contains black iron oxide, hypromellose, red iron oxide, titanium dioxide, and yellow iron oxide. The printing ink contains propylene glycol, shellac, and titanium dioxide.

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For more information, go to www.WILSERDLY.com or call 1-877-436-3683.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 11/2026