

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ELAHERE™ (mirvetuximab soravtansine-gynx) injection, for intravenous use

Initial U.S. Approval: 2022

WARNING: OCULAR TOXICITY

See full prescribing information for complete boxed warning.

- ELAHERE can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis. (5.1, 6.1)
- Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated. (2.3)
- Administer prophylactic artificial tears and ophthalmic topical steroids. (2.3, 5.1)
- Withhold ELAHERE for ocular toxicities until improvement and resume at the same or reduced dose. (2.4, 5.1)
- Discontinue ELAHERE for Grade 4 ocular toxicities. (2.4, 5.1)

INDICATIONS AND USAGE

ELAHERE is a folate receptor alpha (FR α)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with FR α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test. (1, 2.1)

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1, 14)

DOSAGE AND ADMINISTRATION

- Administer ELAHERE as an intravenous infusion only after dilution in 5% Dextrose Injection, USP. ELAHERE is incompatible with normal saline. (2.5)
- The recommended dose of ELAHERE is 6 mg/kg adjusted ideal body weight administered as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. (2.2)
- Premedicate with a corticosteroid, antihistamine, and antipyretic. (2.3)
- Premedicate with an antiemetic, ophthalmic topical steroids, and

lubricating eye drops. (2.3, 5.1)

- See full Prescribing Information for preparation and administration instructions and dose modifications for adverse reactions. (2)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/20 mL (5 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Pneumonitis: Withhold ELAHERE for persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue ELAHERE for Grade 3 or 4 pneumonitis. (2.4, 5.2)
- Peripheral Neuropathy: Monitor patients for new or worsening peripheral neuropathy. Withhold dosage, dose reduce, or permanently discontinue ELAHERE based on the severity of peripheral neuropathy. (2.4, 5.3)
- Embryo-Fetal Toxicity: ELAHERE can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were vision impairment, fatigue, increased aspartate aminotransferase, nausea, increased alanine aminotransferase, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neutrophils, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ImmunoGen at 1-833-486-4646 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: Closely monitor for ELAHERE adverse reactions. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Moderate or severe hepatic impairment: Avoid use. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dosage
- 2.3 Premedication and Prophylactic Regimen
- 2.4 Dosage Modifications
- 2.5 Instructions for Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Ocular Disorders
- 5.2 Pneumonitis
- 5.3 Peripheral Neuropathy
- 5.4 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on ELAHERE

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: OCULAR TOXICITY

- ELAHERE can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].
- Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated [see *Dosage and Administration (2.3)*].
- Administer prophylactic artificial tears and ophthalmic topical steroids [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1)*].
- Withhold ELAHERE for ocular toxicities until improvement and resume at the same or reduced dose [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.1)*].
- Discontinue ELAHERE for Grade 4 ocular toxicities [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

ELAHERE™ is indicated for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test [see *Dosage and Administration (2.1)*].

This indication is approved under accelerated approval based on tumor response rate and durability of response [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer with ELAHERE based on the presence of FR α tumor expression [see *Indications & Usage (1)* and *Clinical Studies (14)*] using an FDA-approved test.

Information on FDA-approved tests for the measurement of FR α tumor expression is available at <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended dose of ELAHERE is 6 mg/kg adjusted ideal body weight (AIBW) administered once every 3 weeks (21-day cycle) as an intravenous infusion until disease progression or unacceptable toxicity [see *Dosage and Administration (2.5)*].

The total dose of ELAHERE is calculated based on each patient's AIBW using the following formula:

$$\text{AIBW} = \text{Ideal Body Weight (IBW [kg])} + 0.4 * (\text{Actual weight [kg]} - \text{IBW})$$

$$\text{Female IBW (kg)} = 0.9 * \text{height(cm)} - 92$$

2.3 Premedication and Required Eye Care

Premedication

Administer the premedications in Table 1 prior to each infusion of ELAHERE to reduce the incidence and severity of infusion related reactions (IRRs), nausea, and vomiting.

Table 1: Premedication Prior to Each ELAHERE Infusion

Premedication	Route of Administration	Examples (or equivalent)	Administration Time Prior to ELAHERE Infusion
Corticosteroid	intravenous	dexamethasone 10 mg	At least 30 minutes prior
Antihistamine	oral or intravenous	diphenhydramine 25 mg to 50 mg	
Antipyretic	oral or intravenous	acetaminophen 325 mg to 650 mg	
Antiemetic	oral or intravenous	5-HT ₃ serotonin receptor antagonist or appropriate alternatives	Before each dose and thereafter as needed

Consider additional premedications including corticosteroids the day prior to ELAHERE administration for patients who experienced IRRs.

Ophthalmic Exams and Premedication

Ophthalmic exam: Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated.

Ophthalmic Topical Steroids: The use of ophthalmic topical steroids is recommended. The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp.

Administer one drop of ophthalmic topical steroids in each eye 6 times daily starting the day prior to each infusion until day 4; then administer one drop in each eye 4 times daily for days 5-8 of each cycle of ELAHERE [see *Warnings and Precautions* (5.1)].

Lubricating Eye Drops: The use of lubricating eye drops at least four times daily and as needed is recommended during treatment with ELAHERE. Instruct patients to use lubricating eye drops and advise to wait at least 10 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops [see *Warnings and Precautions* (5.1)].

2.4 Dosage Modifications

Table 2 provides dose reductions and modifications for adverse reactions. Adjust the schedule of administration to maintain a 3-week interval between doses.

Table 2: Dosage Reduction Schedule

	ELAHERE Dose Levels
Starting Dose	6 mg/kg AIBW
First Dose Reduction	5 mg/kg AIBW
Second Dose Reduction	4 mg/kg AIBW*

* Permanently discontinue in patients who cannot tolerate 4 mg/kg AIBW.

Table 3: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction*	Dosage Modification
Keratitis/Keratopathy <i>[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]</i>	Nonconfluent superficial keratitis	Monitor.
	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	Withhold dose until improved or resolved, then maintain at same dose level or consider dose reduction.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	Withhold dose until improved or resolved, then reduce by one dose level.
	Corneal perforation	Permanently discontinue.
Uveitis <i>[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]</i>	Grade 1/ Rare cell in anterior chamber	Monitor.
	Grade 2/ 1-2+ Cell or Flare in anterior chamber	Withhold dose until Grade 1 or less, then maintain dose at same dose level.
	Grade 3/ 3+ Cell or Flare in anterior chamber	Withhold dose until Grade 1 or less, then reduce dose by one dose level.
	Grade 4/ Hypopyon	Permanently discontinue.
Pneumonitis <i>[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]</i>	Grade 1	Monitor.
	Grade 2	Withhold dose until Grade 1 or less, then resume at same dose level or one lower dose level at the discretion of the healthcare provider.
	Grade 3 or 4	Permanently discontinue.
Peripheral Neuropathy <i>[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]</i>	Grade 2	Withhold dose until Grade 1 or less, then reduce by one dose level.
	Grade 3 or 4	Permanently discontinue.
Infusion-Related Reactions/Hypersensitivity <i>[see Adverse Reactions (6.1)]</i>	Grade 1	Maintain infusion rate.
	Grade 2	- Interrupt infusion and administer supportive treatment. - After recovery from symptoms, resume the infusion at 50% of the previous rate, and if no further symptoms appear, increase rate as appropriate until infusion is completed <i>[see Dosage and Administration (2.5)]</i>. - Administer additional premedication for future cycles <i>[see Dosage and Administration (2.3)]</i>.

Adverse Reaction	Severity of Adverse Reaction*	Dosage Modification
	Grade 3 or 4	- Immediately stop infusion and administer supportive treatment. - Advise patient to seek emergency treatment and immediately notify their healthcare provider if the infusion-related symptoms recur. - Permanently discontinue.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3	Withhold dose until Grade 1 or less, then resume at one lower dose level.
	Grade 4	Permanently discontinue.

* Unless otherwise specified, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

2.5 Instructions for Preparation and Administration

Preparation

- ELAHERE is a hazardous drug. Follow applicable special handling and disposal procedures¹.
- Calculate the dose (mg) (based on the patient's AIBW), total volume (mL) of solution required, and the number of vials of ELAHERE needed [see Recommended Dosage (2.2) and Dose Modifications (2.4)]. More than one vial will be needed for a full dose.
- Remove the vials of ELAHERE from the refrigerator and allow to warm to room temperature.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ELAHERE is a clear to slightly opalescent, colorless solution.
- Gently swirl and inspect each vial prior to withdrawing the calculated dose volume of ELAHERE for subsequent further dilution. *Do not shake* the vial.
- Using aseptic technique, withdraw the calculated dose volume of ELAHERE for subsequent further dilution.
- ELAHERE contains no preservatives and is intended for single-dose only. Discard any unused drug remaining in the vial.

Dilution

- ELAHERE must be diluted prior to administration with 5% Dextrose Injection, USP to a final concentration of 1 mg/mL to 2 mg/mL.
- ELAHERE is incompatible with 0.9% Sodium Chloride Injection. ELAHERE must not be mixed with any other drugs or intravenous fluids.
- Determine the volume of 5% Dextrose Injection, USP required to achieve the final diluted drug concentration. Either remove excess 5% Dextrose Injection, USP from a prefilled intravenous bag or add the calculated volume of 5% Dextrose Injection, USP to a sterile empty intravenous bag. Then add the calculated dose volume of ELAHERE to the intravenous bag.
- Gently mix the diluted drug solution by slowly inverting the bag several times to assure uniform mixing. *Do not shake or agitate*.
- If the diluted infusion solution is not used immediately, store solution either at ambient temperature [(18°C to 25°C (64.4°F to 77°F))] for no more than 8 hours (including infusion time), or under

refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 12 hours. If refrigerated, allow the infusion bag to reach room temperature prior to administration. After refrigeration, administer diluted infusion solutions within 8 hours (including infusion time).

- Do not freeze prepared infusion solution.

Administration

- Inspect the ELAHERE intravenous infusion bag visually for particulate matter and discoloration prior to administration.
- Administer pre-medications prior to ELAHERE administration [*see Premedication and Prophylactic Regimen (2.3)*].
- Administer ELAHERE as an intravenous infusion only, using a 0.2 or 0.22 µm polyethersulfone (PES) in-line filter. Do not substitute other membrane materials.
- Administer the initial dose as an intravenous infusion at the rate of 1 mg/min. If well tolerated after 30 minutes at 1 mg/min, the infusion rate can be increased to 3 mg/min. If well tolerated after 30 minutes at 3 mg/min, the infusion rate can be increased to 5 mg/min.
- If no infusion-related reactions occur with the previous dose, subsequent infusions should be started at the maximally tolerated rate and may be increased up to a maximum infusion rate of 5 mg/min, as tolerated.
- Following the infusion, flush the intravenous line with 5% Dextrose Injection, USP to ensure delivery of the full dose. Do not use any other intravenous fluids for flushing.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) clear to slightly opalescent, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Disorders

ELAHERE can cause severe ocular adverse reactions, including visual impairment, keratopathy (corneal disorders), dry eye, photophobia, eye pain, and uveitis.

Ocular adverse reactions occurred in 61% of patients with ovarian cancer treated with ELAHERE. Nine percent (9%) of patients experienced Grade 3 ocular adverse reactions, including visual impairment, keratopathy/keratitis (corneal disorders), dry eye, photophobia, and eye pain; and one patient (0.2%) experienced Grade 4 keratopathy. The most common ($\geq 5\%$) ocular adverse reactions were visual impairment (49%), keratopathy (36%), dry eye (26%), cataract (15%), photophobia (13%), and eye pain (12%) [*see Adverse Reactions (6.1)*].

The median time to onset for first ocular adverse reaction was 1.2 months (range: 0.03 to 12.9). Of the patients who experienced ocular events, 49% had complete resolution and 39% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade) at last follow up. Ocular adverse reactions led to permanent discontinuation of ELAHERE in 0.6% of patients.

Premedication and use of lubricating and ophthalmic topical steroid eye drops during treatment with ELAHERE are recommended [*see Dosage and Administration (2.3)*]. Advise patients to avoid use of contact lenses during treatment with ELAHERE unless directed by a healthcare provider.

Refer patients to an eye care professional for an ophthalmic exam including visual acuity and slit lamp exam prior to treatment initiation, every other cycle for the first 8 cycles, and as clinically indicated. Promptly refer patients to an eye care professional for any new or worsening ocular signs and symptoms.

Monitor for ocular toxicity and withhold, reduce, or permanently discontinue ELAHERE based on severity and persistence of ocular adverse reactions. [see *Dosage and Administration* (2.4)].

5.2 Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ELAHERE.

Pneumonitis occurred in 10% of patients treated with ELAHERE, including 0.8% with Grade 3 events, and 1 patient (0.2%) with a Grade 4 event. One patient (0.2%) died due to respiratory failure in the setting of pneumonitis and lung metastases. Pneumonitis resulted in ELAHERE dose reduction in 1%, dose interruptions in 3%, and permanent discontinuation in 3% of patients.

Monitor patients for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded through appropriate investigations. Withhold ELAHERE for patients who develop persistent or recurrent Grade 2 pneumonitis until symptoms resolve to $\leq$ Grade 1 and consider dose reduction. Permanently discontinue ELAHERE in all patients with Grade 3 or 4 pneumonitis [see *Dosage and Administration* (2.4)]. Patients who are asymptomatic may continue dosing of ELAHERE with close monitoring.

5.3 Peripheral Neuropathy

Peripheral neuropathy occurred in 36% of patients with ovarian cancer treated with ELAHERE across clinical trials; 2% of patients experienced Grade 3 peripheral neuropathy. Peripheral neuropathy adverse reactions included peripheral neuropathy (19%), peripheral sensory neuropathy (9%), paraesthesia (6%), neurotoxicity (3%), hypoaesthesia (2%), peripheral motor neuropathy (1%), neuralgia (0.4%), polyneuropathy (0.2%) and oral hypoaesthesia (0.2%).

The median time to onset of peripheral neuropathy was 1.3 months (range 0.03 to 29.1). Of the patients who experienced peripheral neuropathy, 28% had complete resolution and 13% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade) at last follow up. Peripheral neuropathy led to discontinuation of ELAHERE in 0.4% of patients.

Monitor patients for signs and symptoms of neuropathy, such as paresthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. For patients experiencing new or worsening peripheral neuropathy, withhold dosage, dose reduce, or permanently discontinue ELAHERE based on the severity of peripheral neuropathy [see *Dosage and Administration* (2.4)].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ELAHERE can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ELAHERE and for 7 months after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Ocular Disorders [see *Warnings and Precautions* (5.1)].

- Pneumonitis [see *Warnings and Precautions* (5.2)].
- Peripheral Neuropathy [see *Warnings and Precautions* (5.3)].

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.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflect exposure to ELAHERE in 464 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer at 6 mg/kg AIBW administered intravenously once every 3 weeks until disease progression or unacceptable toxicity in Study 0417; Study 0403 (NCT02631876), and Study 0401 (NCT01609556). The median duration of treatment was 4.3 months (range: 0.7 to 30.4).

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study 0417

The safety of ELAHERE was evaluated in Study 0417, a single-arm, open-label study in patients (n=106) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer [see *Clinical Studies* (14)]. Patients received ELAHERE 6 mg/kg AIBW once every 3 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 4.2 months (range: 0.7 to 13.3).

Serious adverse reactions occurred in 31% of patients. The most common ($\geq 2\%$) serious adverse reactions were intestinal obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). Fatal adverse reactions occurred in 2% of patients, including small intestinal obstruction (1%) and pneumonitis (1%).

Permanent discontinuation of ELAHERE due to adverse reactions occurred in 11% of patients. The most common ($\geq 2\%$) adverse reactions leading to permanent discontinuation were intestinal obstruction (2%) and thrombocytopenia (2%). One patient (0.9%) permanently discontinued ELAHERE due to visual impairment (unilateral decrease to BCVA $\leq 20/200$ that resolved to baseline after discontinuation).

Dosage delays of ELAHERE due to an adverse reaction occurred in 39% of patients treated with ELAHERE. Adverse reactions which required dosage delays in $\geq 3\%$ of patients included visual impairment (15%), keratopathy (11%), neutropenia (6%), dry eye (5%), cataracts (3%), and increased gamma-glutamyltransferase (3%).

Dose reductions of ELAHERE due to an adverse reaction occurred in 20% of patients. Adverse reactions which required dose reductions in $\geq 3\%$ of patients included visual impairment (9%) and keratopathy (7%).

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were vision impairment, fatigue, increased aspartate aminotransferase, nausea, increased alanine aminotransferase, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neutrophils, and decreased hemoglobin.

Table 4 summarizes the adverse reactions ($\geq 10\%$) in patients treated with ELAHERE in Study 0417.

Table 4: Adverse Reactions (≥10%) in Patients with Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Received ELAHERE in Study 0417

Adverse Reaction	All Grades N=106 (%)	Grade 3-4 N=106 (%)
Eye disorders		
Vision impairment [※]	50	7
Keratopathy [†]	37	9
Dry eye [‡]	27	2
Cataract	18	3
Photophobia	17	0
Eye Pain [§]	10	0
General disorders		
Fatigue	49	3
Gastrointestinal disorders		
Nausea	40	0
Abdominal Pain [*]	36	7
Diarrhea	31	3
Constipation	30	1
Vomiting	19	0
Abdominal distension	11	0
Nervous system disorders		
Peripheral neuropathy [¶]	33	2
Metabolism and nutrition disorders		
Decreased appetite	18	1
Musculoskeletal and connective tissue disorders		
Arthralgia	17	0
Myalgia	10	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea [^]	12	0

※ Visual Impairment includes vision blurred, vitreous floaters, visual acuity reduced, diplopia, presbyopia, accommodation disorder, visual impairment, and refraction disorder.

† Keratopathy includes corneal disorder, corneal epithelial microcysts, corneal epithelial defect, keratitis, keratopathy, corneal deposits, and punctate keratitis.

‡ Dry eye includes dry eye and lacrimation increased.

§ Eye pain includes eye pain and ocular discomfort.

¶ Fatigue includes fatigue and asthenia.

* Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort.

¶ Peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, and neurotoxicity.

^ Dyspnea includes dyspnea and exertional dyspnea.

Clinically relevant adverse reactions occurring in <10% of patients who received ELAHERE in Study 0417 included infusion related reactions/hypersensitivity (9%), pneumonitis (8%), thrombocytopenia (5%), and uveitis (1%).

Table 5 summarizes the laboratory abnormalities in Study 0417.

Table 5: Select Laboratory Abnormalities $\geq 10\%$ for All Grades, or $\geq 2\%$ for Grades 3-4 in Patients Who Received ELAHERE

Laboratory Abnormality	ELAHERE*	
	All Grades (%)	Grade 3-4 (%)
Liver Function Tests		
Increased aspartate aminotransferase	50	2
Increased alanine aminotransferase	39	2
Increased alkaline phosphatase	30	1
Hematology*		
Decreased lymphocytes	35	7
Decreased leukocytes	26	1
Decreased neutrophils	26	3
Decreased hemoglobin	25	3
Decreased platelets	18	2
Chemistry		
Decreased albumin	31	1
Decreased magnesium	27	2
Increased creatinine	16	0
Decreased potassium	15	4

* The denominator used to calculate the rate varied from 98 to 101 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 ELAHERE

Strong CYP3A4 Inhibitors

DM4 is a CYP3A4 substrate. Concomitant use of ELAHERE with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of ELAHERE adverse reactions [see *Adverse Reactions (6)*]. Closely monitor patients for adverse reactions with ELAHERE when used concomitantly with strong CYP3A4 inhibitors [see *Warnings and Precautions (5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ELAHERE can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells [see *Clinical Pharmacology* (12.1), *Nonclinical Toxicology* (13.1)]. Human immunoglobulin G (IgG) is known to cross the placental barrier; therefore, ELAHERE has the potential to be transmitted from the mother to the developing fetus. There are no available human data on ELAHERE use in pregnant women to inform a drug-associated risk. No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine-gynx. Advise patients of the potential risk to a fetus.

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

Data

Animal Data: No reproductive or developmental animal toxicity studies have been conducted with mirvetuximab soravtansine-gynx. The cytotoxic component of ELAHERE, DM4, disrupts microtubule function, is genotoxic, and can be toxic to actively dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

8.2 Lactation

Risk Summary

There are no data on the presence of mirvetuximab soravtansine-gynx in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ELAHERE and for 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with ELAHERE and for 7 months after the last dose.

8.4 Pediatric Use

Safety and effectiveness of ELAHERE have not been established in pediatric patients.

8.5 Geriatric Use

Of the 106 patients who were treated in Study 0417, 44% of patients were ≥ 65 years old. Grade ≥ 3 adverse reactions occurred in 49% of patients ≥ 65 years and in 51% < 65 years. No clinically meaningful differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of ELAHERE [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dosage adjustment of ELAHERE is recommended for patients with mild to moderate renal impairment (CL_{cr} 30 to 90 mL/min). The effect of severe renal impairment (CL_{cr} 15 to < 30 mL/min) or end-stage renal disease on ELAHERE is unknown [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

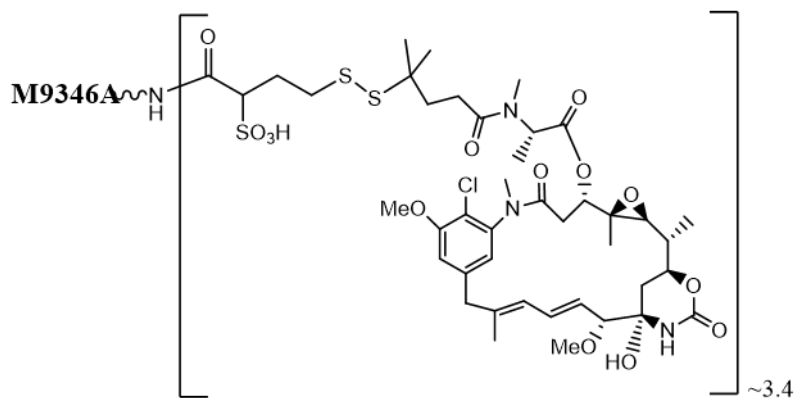
Avoid use of ELAHERE in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN).

No dosage adjustment of ELAHERE is recommended for patients with mild hepatic impairment (total bilirubin $\leq$ ULN and AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Mirvetuximab soravtansine-gynx is a folate receptor alpha (FR α)-directed antibody-drug conjugate (ADC) consisting of three components: 1) an anti-FR α monoclonal antibody of IgG1 subtype 2) the small molecule anti-tubulin agent DM4 (a maytansine derivative) and 3) a linker, sulfo-SPDB (1-(2,5-dioxopyrrolidin-1-yl)oxy-1-oxo-4-(pyridin-2-yl)disulfanyl)butane-2-sulfonic acid) that covalently attaches DM4 to the mirvetuximab antibody. Mirvetuximab soravtansine-gynx has an approximate molecular weight of 150 kDa. An average of 3.4 molecules of DM4 are attached to each antibody molecule. Mirvetuximab soravtansine-gynx is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

Mirvetuximab soravtansine-gynx has the following structure:



ELAHERE (mirvetuximab soravtansine-gynx) injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless solution containing 100 mg/20 mL of mirvetuximab soravtansine-gynx in single-dose vials. Each mL of solution contains 5 mg of mirvetuximab soravtansine-gynx, and glacial acetic acid (0.22 mg), polysorbate 20 (0.1 mg), sodium acetate (0.53 mg), sucrose (90 mg), and Water for Injection. The pH is approximately 5.0.

The ELAHERE vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mirvetuximab soravtansine-gynx is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against folate receptor alpha (FR α). The small molecule, DM4, is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FR α , mirvetuximab soravtansine-gynx is internalized followed by intracellular release of DM4 via proteolytic cleavage. DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.

12.2 Pharmacodynamics

Exposure-Response Relationships

An exposure-response relationship between mirvetuximab soravtansine-gynx and overall response rates was observed. Higher incidence of Grade ≥ 2 ocular adverse reactions and Grade ≥ 2 peripheral neuropathy occurred with increasing mirvetuximab soravtansine-gynx exposure.

Cardiac Electrophysiology

At the approved recommended dose, ELAHERE did not cause large mean increases (>10 msec) in the QTc interval.

12.3 Pharmacokinetics

The pharmacokinetics were characterized after patients were administered mirvetuximab soravtansine-gynx 0.161 mg/kg to 8.71 mg/kg adjusted ideal body weight (AIBW) dosages, (0.0268 times to 1.45 times the approved recommended dosage of 6 mg/kg AIBW), unless otherwise noted.

Table 6 summarizes the exposure parameters of mirvetuximab soravtansine-gynx, unconjugated DM4, and its metabolite S-methyl-DM4 following administration after the first cycle (3-weeks) of mirvetuximab soravtansine-gynx 6 mg/kg to patients. Peak mirvetuximab soravtansine-gynx concentrations were observed near the end of intravenous infusion, while peak unconjugated DM4 concentrations were observed on the second day after administration of mirvetuximab soravtansine-gynx, and the peak S-methyl-DM4 concentrations were observed approximately 3 days after administration of mirvetuximab soravtansine-gynx. Steady state concentrations of mirvetuximab soravtansine-gynx, DM4, and S-methyl-DM4 were reached after 1 treatment cycle. Accumulation of the mirvetuximab soravtansine-gynx, DM4, and S-methyl-DM4 was minimal following repeat administration of mirvetuximab soravtansine-gynx.

Table 6: Exposure Parameters of Mirvetuximab Soravtansine-gynx, Unconjugated DM4, and S-methyl DM4 After First Treatment Cycle of 6 mg/kg of Mirvetuximab Soravtansine-gynx

	Mirvetuximab Soravtansine-gynx Mean ($\pm$SD)	Unconjugated DM4 Mean ($\pm$SD)	S-methyl-DM4 Mean ($\pm$SD)
$C_{\max}$	137.3 ($\pm$ 62.3) μ g/mL	4.11 ($\pm$ 2.29) ng/mL	6.98 ($\pm$ 6.79) ng/mL
AUC_{τ}	20.65 ($\pm$ 6.84) h*mg/mL	530 ($\pm$ 245) h*ng/mL	1848 ($\pm$ 1585) h*ng/mL

$C_{\max}$ = maximum concentration, AUC_{τ} = area under the concentration vs. time curve over the dosing interval (21 days).

Distribution

The mean ($\pm$ SD) steady state volume of distribution of mirvetuximab soravtansine-gynx was 2.63 ($\pm$ 2.98) L.

Human plasma protein binding of DM4 and S-methyl DM4 was $>99\%$, in vitro.

Elimination

Total plasma clearance (geometric mean [CV%]) of mirvetuximab soravtansine-gynx was 18.9 mL/hour (51.9%). The geometric mean terminal phase half-life of mirvetuximab soravtansine-gynx after the first dose was 4.8 days leading to a steady state at approximately 24 days. For the unconjugated DM4, the total plasma clearance (geometric mean [CV%]) was 13.8 L/hour (31.1%) and the geometric mean terminal phase half-life was 2.8 days. For S-methyl-DM4, the total plasma clearance (geometric mean [CV%]) was 4.3 L/hour (63.6%) and the geometric mean terminal phase half-life was 5.0 days.

Metabolism

The monoclonal antibody portion of mirvetuximab soravtansine-gynx is expected to be metabolized into small peptides by catabolic pathways. Unconjugated DM4 and S-methyl-DM4 undergo metabolism by CYP3A4. In

human plasma, DM4 and S-methyl DM4 were identified as the main circulating metabolites, accounting for approximately 0.4% and 1.4% of mirvetuximab soravtansine-gynx AUCs, respectively.

Excretion

S-methyl DM4 and DM4-sulfo-SPDB-lysine were detected in urine within 24 hours of infusion as the main metabolites.

Specific Populations

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine-gynx were observed based on age (34 to 89 years), body weight (36 to 136 kg), mild hepatic impairment (total bilirubin $\leq$ ULN and any AST $>$ ULN or total bilirubin >1 to 1.5 times ULN and any AST), or mild to moderate renal impairment (CLcr ≥ 30 and <90 mL/min).

The pharmacokinetics of ELAHERE in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) or severe renal impairment (CLcr 15 to 30 mL/min) is unknown.

Drug Interaction Studies

Clinical studies and model informed approaches

No clinical studies evaluating the drug-drug interaction potential of mirvetuximab soravtansine-gynx have been conducted.

However, in 3 clinical trials, there were no differences in exposure between patients who received concomitant weak or moderate CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors and those who did not.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Unconjugated DM4 is a time-dependent inhibitor of CYP3A4.

Unconjugated DM4 and S-methyl DM4 are not direct inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. DM4 and S-methyl DM4 are not inducers of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Unconjugated DM4 and S-methyl DM4 are substrates of P-gp but are not inhibitors of P-gp.

12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation against mirvetuximab soravtansine-gynx is highly dependent on the sensitivity and specificity of the assay. The observed incidence of anti-drug antibodies (including neutralizing antibody) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies to mirvetuximab soravtansine-gynx in other studies.

With a median duration of treatment of 4.3 months in Studies 0417, 0401, and 0403, a total of 55/423 (13%) ovarian cancer patients treated with mirvetuximab soravtansine-gynx at 6 mg/kg AIBW had at least 1 post-baseline positive sample for anti-mirvetuximab soravtansine-gynx antibodies. Of those patients, 28/423 patients (7%) had developed treatment-emergent ADA and 3/423 patients (0.7%) had treatment-enhanced ADA. Neutralizing antibodies were detected in 24/423 (6%) of patients.

Because of the low occurrence of anti-mirvetuximab soravtansine-gynx antibodies, the effect of these antibodies on the pharmacokinetics, efficacy, and/or safety of mirvetuximab soravtansine-gynx is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with mirvetuximab soravtansine-gynx or DM4.

DM4 and the metabolite, S-methyl DM4, were clastogenic in the in vivo rat bone marrow micronucleus study. DM4 and S-methyl DM4 were not mutagenic in the bacterial reverse mutation (Ames) assay.

Fertility studies have not been conducted with mirvetuximab soravtansine-gynx or DM4.

14 CLINICAL STUDIES

The efficacy of ELAHERE was evaluated in Study 0417 (NCT04296890), a single-arm trial of patients with FR α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (n=106). Patients were permitted to receive up to three prior lines of systemic therapy. All patients were required to have received prior bevacizumab. The trial enrolled patients whose tumors were positive for FR α expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Patients were excluded if they had corneal disorders, ocular conditions requiring ongoing treatment, Grade >1 peripheral neuropathy, or noninfectious interstitial lung disease.

Patients received ELAHERE 6 mg/kg (based on adjusted ideal body weight) as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter.

The major efficacy outcome measures were investigator-assessed overall response rate (ORR) and duration of response (DOR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

The efficacy evaluable population included 104 patients with platinum-resistant disease, who had measurable disease, and received at least one dose of ELAHERE. In these 104 patients, the median age was 62 years (range: 35 to 85); 96% were White, 2% were Asian, and 2% did not have race reported. Two percent of patients were Hispanic or Latino. All patients had an ECOG PS of 0 (57%) or 1 (43%). Ten percent of patients had received 1 prior line of systemic therapy, 39% of patients had received 2 prior lines of systemic therapy, and 50% of patients had received 3 prior lines of systemic therapy. All patients had received prior bevacizumab and 47% had received a prior PARP inhibitor.

Efficacy results for Study 0417 are summarized in Table 7.

Table 7: Efficacy Results in Study 0417

	ELAHERE (N=104)
Confirmed Overall Response Rate^a (95% CI)	31.7% (22.9, 41.6)
Complete response rate	4.8%
Partial response rate	26.9%
Duration of Response	N=33
Median duration of response, months (95% CI)	6.9 (5.6, 9.7)

^a Investigator assessment.

Response assessment results using independent radiology review were consistent with investigator assessment.

15 REFERENCES

¹“OSHA Hazardous Drugs.” OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each ELAHERE (mirvetuximab soravtansine-gynx) injection carton (NDC 72903-853-01) contains:

- One single-dose vial containing 100 mg of mirvetuximab soravtansine-gynx in 20 mL (5 mg/mL) of clear to slightly opalescent, colorless sterile solution.

Storage and Handling

Store ELAHERE vials upright in a refrigerator at 2°C to 8°C (36°F to 46°F) until the time of preparation in the original carton to protect from light.

Do not freeze or shake.

ELAHERE is a hazardous drug. Follow applicable special handling and disposal procedures¹.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Disorders

Inform patients about the need for eye exams before and during treatment with ELAHERE.

Advise patients to contact their healthcare provider promptly if they experience any visual changes. Advise patients to use steroid eye drops and artificial tear substitutes [see *Dosage and Administration* (2.3) and *Warnings and Precautions* (5.1)].

Pneumonitis

Advise patients to immediately report new or worsening respiratory symptoms [see *Dosage and Administration* (2.3) and *Warnings and Precautions* (5.2)].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise female patients to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations* (5.4, 8.1, 8.3)].

Advise females of reproductive potential to use effective contraception during treatment with ELAHERE and for 7 months after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

Lactation

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

Manufactured by:
ImmunoGen, Inc.
Waltham, MA 02451
1-781-895-0600
U.S. License 2288

ELAHERE is a trademark of ImmunoGen, Inc.
©2022 ImmunoGen, Inc.

All rights reserved.