ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ELAHERE 5 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 5 mg of mirvetuximab soravtansine.
One vial contains 100 mg mirvetuximab soravtansine in 20 mL.

Mirvetuximab soravtansine is a FRα-directed antibody-drug conjugate (ADC). The ADC consists of an anti-FRα monoclonal antibody of IgG1 subtype produced using recombinant DNA technology in Chinese Hamster Ovary cells and attached via a cleavable linker (butanoic acid, 4-(2-pyridinyldithio)-2-sulfo-1-(2,5-dioxo-1-pyrrolidinyl) ester) to a maytansinoid DM4, an anti-tubulin agent. Mirvetuximab soravtansine contains an average of 3.4 DM4 payload molecules bound to the anti-FRα antibody.

Excipients with known effect

This medicinal product contains 2.11 mg of polysorbate 20 in each vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELAHERE as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (see section 4.2).

4.2 Posology and method of administration

ELAHERE must be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patient selection

Eligible patients should have FRα tumour status defined as ≥75% viable tumour cells demonstrating moderate (2+) and/or strong (3+) membrane staining by immunohistochemistry (IHC), assessed by a CE-marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If a CE-marked IVD is not available, an alternative validated test should be used.

Posology

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. Dosing based on AIBW reduces exposure variability for patients who are either underweight or overweight.

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

AIBW = Ideal Body Weight (IBW [kg]) + 0.4*(Actual weight [kg] – IBW)
Female IBW [kg] = 0.9*height [cm] – 92

For a female patient who is 165 cm in height and 80 kg in weight

First, calculate IBW:	IBW = 0.9 * 165 – 92 = 56.5 kg
Then calculate AIBW:	AIBW = 56.5 + 0.4 * (80 – 56.5) = 65.9 kg

Pre-medication

Pre-medication for infusion related reactions (IRRs), nausea, and vomiting

Administer the pre-medications in Table 1 prior to each infusion of ELAHERE to reduce the incidence and severity of IRRs, nausea, and vomiting.

Table 1: Pre-medication prior to each ELAHERE infusion

Pre-medication	**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 or paracetamol 325 mg to 650 mg	
Antiemetic	oral or intravenous	5-HT_3 serotonin receptor antagonist or appropriate alternatives	before each dose and following the administration of other premedication

For patients experiencing nausea and/or vomiting, additional antiemetics may be considered thereafter as needed.

For patients who experience an IRR Grade ≥2, additional pre-medication with dexamethasone 8 mg two times a day (BID) (or equivalent) the day before ELAHERE administration should be considered.

Ophthalmic exam and pre-medication

Ophthalmic exam: An ophthalmic exam including visual acuity and slit lamp exam should be conducted before the initiation of ELAHERE and if a patient develops any new or worsening ocular symptoms prior to the next dose. In patients with ≥ Grade 2 ocular adverse reactions, additional ophthalmic exams should be conducted at a minimum of every other cycle and as clinically indicated until resolution or return to baseline.

Ophthalmic topical steroids: For patients found to have signs of ≥ Grade 2 corneal adverse reactions (keratopathy) on slit lamp examination, secondary prophylaxis with ophthalmic topical steroids is recommended for subsequent cycles of ELAHERE, unless the patient's eye care professional determines that the risks outweigh the benefits of such therapy.

- Patients should be instructed to use steroid eye drops on the day of infusion and through the next 7 days of each subsequent cycle of ELAHERE (see Table 3).
- Patients should be advised to wait at least 15 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops.

During treatment with ophthalmic topical steroids the measurement of intraocular pressure and an examination with slit lamp should be carried out regularly.

Lubricating eye drops: It is recommended to instruct patients to use lubricating eye drops throughout treatment with ELAHERE.

Dose modifications

Before the start of each cycle, the patient should be advised to report any new or worsening symptoms to the treating physician or qualified individual.

In patients who develop new or worsening ocular symptoms, an ophthalmic exam should be conducted before dosing. The treating physician should review the patient's ophthalmic examination report before dosing and determine the dose of ELAHERE based on the severity of findings in the most severely affected eye.

Table 2 and Table 3 provide dose reductions and modifications for adverse reactions. The schedule of administration should be maintained at a 3-week interval between the doses.

Table 2: Dose 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: Dose modifications for adverse reactions

Adverse reaction	**Severity of adverse reaction***	**Dose modification**
Keratitis/keratopathy (see sections 4.4 and 4.8)	Non-confluent superficial keratitis/keratopathy	Monitor
	Confluent superficial keratitis/keratopathy, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	Withhold dose until improved to nonconfluent superficial keratitis/keratopathy or better or resolved, then maintain at same dose level. Consider dose reduction for patients with recurrent confluent keratitis/keratopathy despite best supportive care or in patients with ocular toxicity lasting longer than 14 days.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 6/60 or worse	Withhold dose until improved to nonconfluent superficial keratitis/keratopathy or better or resolved, then reduce by one dose level.
	Corneal perforation	Permanently discontinue
Pneumonitis (see sections 4.4 and 4.8)	Grade 1	Monitor
	Grade 2	Withhold dose until Grade 1 or less, then maintain at same dose level or consider dose reduction if recurrent, lasts longer than 28 days, or at physician discretion.

Adverse reaction	Severity of adverse reaction*	Dose modification
	Grade 3 or 4	Permanently discontinue
Peripheral neuropathy (see sections 4.4 and 4.8)	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 (see sections 4.4 and 4.8)	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. • Administer additional pre-medication with dexamethasone 8 mg oral BID the day before infusion (or local equivalent) for future cycles.
	Grade 3 or 4	• Immediately stop infusion and administer supportive treatment. • Advise patient to seek emergency treatment and immediately notify their healthcare professional if the infusion-related symptoms recur after discharge from the infusion area. • Permanently discontinue
Haematological (see section 4.8)	Grade 3 or 4	Withhold dose until Grade 1 or less, then resume at one lower dose level.
Other adverse reactions (see section 4.8)	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.

Special populations

Paediatric population

There is no relevant use of ELAHERE for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer in the paediatric population (see section 5.1).

Elderly

No dose adjustment of ELAHERE is recommended in patients ≥65 years of age (see section 5.2).

Renal impairment

No dose adjustment of ELAHERE is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] 30 to <90 mL/min). ELAHERE has not been evaluated in patients with severe renal impairment (CLcr 15 to <30 mL/min) or end-stage renal disease and the potential need for dose adjustment in these patients cannot be determined (see section 5.2).

Hepatic impairment

No dose adjustment of ELAHERE is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1 to 1.5 times ULN and any AST) (see section 5.2).

ELAHERE should be avoided in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST).

Method of administration

ELAHERE is for intravenous infusion at a rate of 1 mg/min. If well tolerated after 30 minutes, 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.

For incompatibilities, see section 6.2.

ELAHERE requires dilution with 5% glucose for intravenous infusion. For instructions on dilution of the medicinal product before administration, see section 6.6.

ELAHERE must be administered as an intravenous infusion only, using a 0.2 or 0.22 µm polyethersulfone (PES) in-line filter (see Special handling and disposal procedures in section 6.6).

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains a cytotoxic component, which is covalently attached to the monoclonal antibody (see special handling and disposal procedures in section 6.6).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Ocular disorders

Mirvetuximab soravtansine can cause severe ocular adverse reactions, including visual impairment (predominantly blurred vision), keratopathy (corneal disorders), dry eye, photophobia, and eye pain (see sections 4.7 and 4.8).

Patients should be referred to an eye care professional for an ophthalmic exam before initiation of mirvetuximab soravtansine.

Before the start of each cycle, the patient should be advised to report any new or worsening ocular symptoms to the treating physician or qualified individual.

If ocular symptoms develop, an ophthalmic exam should be conducted, the patient's ophthalmic report should be reviewed and the dose of mirvetuximab soravtansine may be modified based on the severity of the findings (see section 4.2).

Use of lubricating eye drops during treatment with mirvetuximab soravtansine is recommended. In patients who develop ≥Grade 2 corneal adverse reactions, ophthalmic topical steroids are recommended for subsequent cycles of mirvetuximab soravtansine (see section 4.2).

The physician should monitor patients for ocular toxicity and withhold, reduce, or permanently discontinue mirvetuximab soravtansine based on the severity and persistence of ocular adverse reactions (see section 4.2).

Patients should be advised to avoid use of contact lenses during treatment with mirvetuximab soravtansine unless directed by a healthcare professional.

Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with mirvetuximab soravtansine (see section 4.8).

Patients should be monitored for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded through appropriate investigations.

Mirvetuximab soravtansine treatment should be withheld for patients who develop persistent or recurrent Grade 2 pneumonitis until symptoms resolve to ≤Grade 1 and dose reduction should be considered. Mirvetuximab soravtansine should be permanently discontinued in all patients with Grade 3 or 4 pneumonitis (see section 4.2). Patients who are asymptomatic may continue dosing of mirvetuximab soravtansine with close monitoring.

Peripheral neuropathy

Peripheral neuropathy has occurred with mirveutximab soravtansine, including Grade ≥3 reactions (see section 4.8).

Patients should be monitored for signs and symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. For patients experiencing new or worsening peripheral neuropathy, mirvetuximab soravtansine dose should be withheld, reduced, or permanently discontinued based on the severity of peripheral neuropathy (see section 4.2).

Embryo-foetal toxicity

Based on its mechanism of action, mirvetuximab soravtansine could cause embryo-foetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells.

Patients of childbearing potential should use effective contraception during treatment with mirvetuximab soravtansine and for 7 months after the last dose (see section 4.6).

Excipients with known effect

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

This medicinal product contains 2.11 mg of polysorbate 20 in each vial.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical drug-drug interaction studies with ELAHERE have not been conducted.

DM4 is a CYP3A4 substrate. Concomitant use of ELAHERE with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure (see section 5.2), which may increase the risk of ELAHERE adverse reactions (see section 4.8). If concomitant use with strong CYP3A4 inhibitors (e.g. ceritinib, clarithromycin, cobicistat, idelalisib, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir, telithromycin, voriconazole) cannot be avoided, patients should be closely monitored for adverse

reactions. Strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine) may decrease the exposure of unconjugated DM4.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status in patients of childbearing potential should be verified prior to initiating mirvetuximab soravtansine treatment.

Patients of childbearing potential should use effective contraception during treatment with mirvetuximab soravtansine and for 7 months after the last dose.

Pregnancy

Based on its mechanism of action, mirvetuximab soravtansine can cause embryo-foetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells (see sections 5.1 and 5.3). Human immunoglobulin G (IgG) is known to cross the placental barrier; therefore, mirvetuximab soravtansine has the potential to be transmitted from the pregnant patient to the developing foetus. There are no available human data on mirvetuximab soravtansine use in pregnant patients to inform a drug-associated risk. No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine.

Administration of ELAHERE to pregnant patients is not recommended, and patients should be informed of the potential risks to the foetus if they become or wish to become pregnant. Patients who become pregnant must immediately contact their doctor. If a patient becomes pregnant during treatment with ELAHERE or within 7 months following the last dose, close monitoring is recommended.

Breast-feeding

It is unknown whether mirvetuximab soravtansine/metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded as human immunoglobulin G (IgG) is known to pass on in breast milk. ELAHERE should not be used during breast-feeding and for 1 month after the last dose.

Fertility

Fertility studies have not been conducted with mirvetuximab soravtansine or DM4. There are no data on the effect of ELAHERE on human fertility. However, given the mechanism of action of ELAHERE leads to microtubule disruption and death of rapidly dividing cells, there is the potential for drug-related fertility effects.

4.7 Effects on the ability to drive and use machines

ELAHERE has moderate influence on the ability to drive and use machines. If patients experience visual disturbances, peripheral neuropathy, fatigue, or dizziness during treatment with mirvetuximab soravtansine, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions with mirvetuximab soravtansine were blurred vision (43%), nausea (41%), diarrhoea (39%), fatigue (35%), abdominal pain (30%), keratopathy (29%), dry eye

(27%), constipation (26%), vomiting (23%), decreased appetite (22%), peripheral neuropathy (20%), headache (19%), asthenia (18%), AST increased (16%), and arthralgia (16%).

The most commonly reported serious adverse reactions were pneumonitis (4%), small intestinal obstruction (3%), intestinal obstruction (3%), pleural effusion (2%), abdominal pain (2%), dehydration (1%), constipation (1%), nausea (1%), ascites (1%) and thrombocytopenia (<1%).

Adverse reactions that most commonly led to dose reduction or dose delay were blurred vision (17%), keratopathy (10%), dry eye (5%), neutropenia (5%), keratitis (4%), cataract (3%), visual acuity reduced (3%), thrombocytopenia (3%), peripheral neuropathy (3%), and pneumonitis (3%).

Permanent discontinuation due to an adverse reaction occurred in 12% of patients who received mirvetuximab soravtansine, including most commonly, gastrointestinal disorders (4%), respiratory, thoracic, and mediastinal disorders (3%), blood and lymphatic system disorders (1%), nervous system disorders (1%), and eye disorders (1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from 4 clinical studies which included 682 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively referenced as Epithelial Ovarian Cancer (EOC) treated with mirvetuximab soravtansine 6 mg/kg AIBW administered once every 3 weeks. The median duration of treatment with mirvetuximab soravtansine was 19.1 weeks (range: 3, 132 weeks).

The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 4: Tabulated list of all grade adverse reactions in patients treated with mirvetuximab soravtansine in clinical studies

System Organ Class	Frequency category	Adverse reactions
Infections and infestations	Very common	Urinary tract infection
Blood and lymphatic system disorders	Very common	Anaemia, thrombocytopenia
	Common	Neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite, hypomagnesaemia
	Common	Hypokalaemia, dehydration
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Peripheral neuropathy[1], headache,
	Common	Dysgeusia, dizziness
Eye disorders	Very common	Keratopathy[2], cataract[3], blurred vision event[4], photophobia, eye pain, dry eye[5]
	Common	Ocular discomfort[6]
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Pneumonitis[7], dyspnoea, cough
Gastrointestinal disorders	Very common	Diarrhoea, abdominal pain[8], constipation, abdominal distension, vomiting, nausea
	Common	Ascites, gastro-oesophageal reflux disease, stomatitis, dyspepsia
Hepatobiliary disorders	Common	Hyperbilirubinaemia

System Organ Class	Frequency category	Adverse reactions
Skin and subcutaneous tissue disorders	Common	Pruritus
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Myalgia, back pain, pain in extremity, muscle spasms
General disorders and administration site conditions	Very common	Fatigue
	Common	Pyrexia
Investigations	Very common	Aspartate aminotransferase increased, alanine aminotransferase increased
	Common	Blood alkaline phosphatase increased, gamma-glutamyl transferase increased, weight decreased
Injury, poisoning and procedural complication	Common	Infusion related reaction/hypersensitivity[9]

[1] Peripheral neuropathy grouped term includes hypoaesthesia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy (see section Description of selected adverse reactions).
[2] Keratopathy group term includes corneal cyst, corneal deposits, corneal disorder, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal opacity, corneal pigmentation, keratitis, keratitis interstitial, keratopathy, limbal stem cell deficiency, and punctate keratitis (see section Description of selected adverse reactions).
[3] Cataract grouped term includes cataract, cataract cortical, and cataract nuclear (see section Description of selected adverse reactions).
[4] Blurred vision event grouped term includes accommodation disorder, diplopia, hypermetropia, presbyopia, refraction disorder, vision blurred, visual impairment, visual acuity reduced, and vitreous floaters (see section Description of selected adverse reactions).
[5] Dry eye grouped term includes dry eye and lacrimation decreased (see section Description of selected adverse reactions).
[6] Ocular discomfort grouped term includes eye irritation, eye pruritus, foreign body sensation in eye, and ocular discomfort (see section Description of selected adverse reactions).
[7] Pneumonitis group term includes interstitial lung disease, organising pneumonia, pneumonitis, pulmonary fibrosis, and respiratory failure (see section Description of selected adverse reactions).
[8] Abdominal pain grouped term includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.
[9] Infusion related reaction/hypersensitivity grouped term includes SMQ Hypersensitivity narrow and flushing, erythema, erythema of eyelid.

Description of selected adverse reactions

Ocular disorders

Ocular adverse reactions (grouped terms) occurred in 59% of patients with EOC treated with mirvetuximab soravtansine. Eleven percent (11%) of patients experienced Grade 3 ocular adverse reactions and <1% experienced Grade 4 events. The most common ≥ Grade 3 ocular adverse reactions were blurred vision and keratopathy (both 5%, grouped terms) and cataract (4%).

The median time to onset for first ocular adverse reaction was 5.1 weeks (range: 0.1 to 68.6). Of the patients who experienced ocular events, 53% had complete resolution (Grade 0) and 38% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade). At the last follow-up, 0.3% (2/682) patients had ≥ Grade 3 ocular adverse events (1 patient with Grade 3 decreased visual acuity and 1 patient with Grade 4 cataract).

Ocular adverse reactions led to dose delays in 24% of patients, and dose reductions in 15% of patients. Ocular adverse reactions led to permanent discontinuation of mirvetuximab soravtansine in 1% of patients.

Pneumonitis

Pneumonitis (grouped terms) occurred in 10% of patients with EOC treated with mirvetuximab soravtansine, including 0.9% (6/682) patients with Grade 3 events, and 0.2% (1/682) patient with a Grade 4 event. Two patients (0.3%) died due to respiratory failure. One patient (0.2%) died due to respiratory failure in the setting of Grade 1 pneumonitis and lung metastases confirmed at autopsy. One patient (0.2%) died due to respiratory failure of unknown aetiology without concurrent pneumonitis.

The median time to onset of pneumonitis was 18.1 weeks (range 1.6 to 97.0). Pneumonitis resulted in mirvetuximab soravtansine dose delays in 3%, dose reductions in 1%, and permanent discontinuation in 3% of patients.

Peripheral neuropathy

Peripheral neuropathy (grouped terms) occurred in 36% of patients with EOC treated with mirvetuximab soravtansine across clinical studies; 3% of patients experienced Grade 3 peripheral neuropathy.

The median time to onset of peripheral neuropathy was 5.9 weeks (range 0.1 to 126.7). Peripheral neuropathy resulted in mirvetuximab soravtansine dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in 0.7% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known treatment/antidote available for overdose of mirvetuximab soravtansine. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates.
ATC code: L01FX26

Mechanism of action

Mirvetuximab soravtansine is an antibody-drug conjugate. The antibody is an engineered IgG1 directed against folate receptor alpha (FRα). The function of the antibody portion is to bind to FRα expressed on the surface of ovarian cancer cells. DM4 is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FRα, mirvetuximab soravtansine is internalised 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.

Pharmacodynamic effects

Cardiac electrophysiology

At the approved recommended dose, mirvetuximab soravtansine did not cause mean increases >10 msec in the QTc interval based on the results of concentration-QTc analysis.

Clinical efficacy and safety

Study IMGN853-0416 (MIRASOL)

The efficacy and safety of mirvetuximab soravtansine were studied in Study IMGN853-0416, a multicentre, open-label, active-controlled, randomised, two-arm phase 3 study that enrolled platinum-resistant advanced high-grade serous epithelial ovarian, primary peritoneal or fallopian tube cancers patients whose tumours (including archival tissue) were FRα positive as determined by the FOLR1 (FOLR1-2.1) RxDx assay (≥75% of viable tumour cells with moderate (2) and/or strong (3) membrane staining intensity by immunohistochemistry (IHC)).

Platinum-resistant disease was defined as EOC that recurred within 6 months of the last dose of platinum.

The study excluded patients with primary platinum-refractory disease, patients with ECOG≥2 and patients with active or chronic corneal disorders, ocular conditions requiring ongoing treatment, Grade ≥2 peripheral neuropathy, or non-infectious ILD/pneumonitis.

Patients were randomised 1:1 to receive either ELAHERE 6 mg/kg AIBW IV (N=227) at Day 1 of each 3-week cycle or one of the following chemotherapies (N=226) as decided by the investigator prior to randomisation:

- Paclitaxel (Pac) 80 mg/m^2 administered once weekly within a 4-week cycle;
- Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 administered once every 4 weeks;
- Topotecan (Topo) 4 mg/m^2 administered on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days at 1.25 mg/m^2 from Days 1-5 of each 21-day cycle

Randomisation was stratified by number of prior lines of therapy (1 vs 2 vs 3) and by Investigator's choice of chemotherapy (IC Chemo) (Pac vs PLD vs Topo). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression free survival (PFS) based on investigator assessment using RECIST 1.1 criteria. Objective response rate (ORR) and overall survival (OS) were key secondary efficacy outcome measures.

In total, 453 patients were randomised. The median age was 63 years (range: 29 to 88 years), and patients were predominantly white (66%; 12% Asian). Most patients (80%) had ovarian cancer of epithelial origin; 11% of the fallopian tube; 8% of primary peritoneal; all (100%) were of high-grade serous histology. Approximately half the patients (47%) received 3 prior systemic therapies, 39% had 2 prior lines, and 14% of patients had 1 prior line. The majority of patients received a prior poly ADP ribose polymerase (PARP) inhibitor (55%) and prior bevacizumab (62%). The platinum-free interval following the most recent line of therapy was ≤3 months in 41% of patients, and 3 to 6 months in 58% of patients. Fifty five percent (55%) of patients had an ECOG performance status of 0, and 44% had an ECOG of 1.

The primary analysis demonstrated a statistically significant improvement in PFS and OS for patients randomised to ELAHERE as compared with IC chemotherapy.

Table 5 summarises the efficacy results of study IMGN853-0416 (MIRASOL).

Table 5: Efficacy results of Study IMGN853-0416

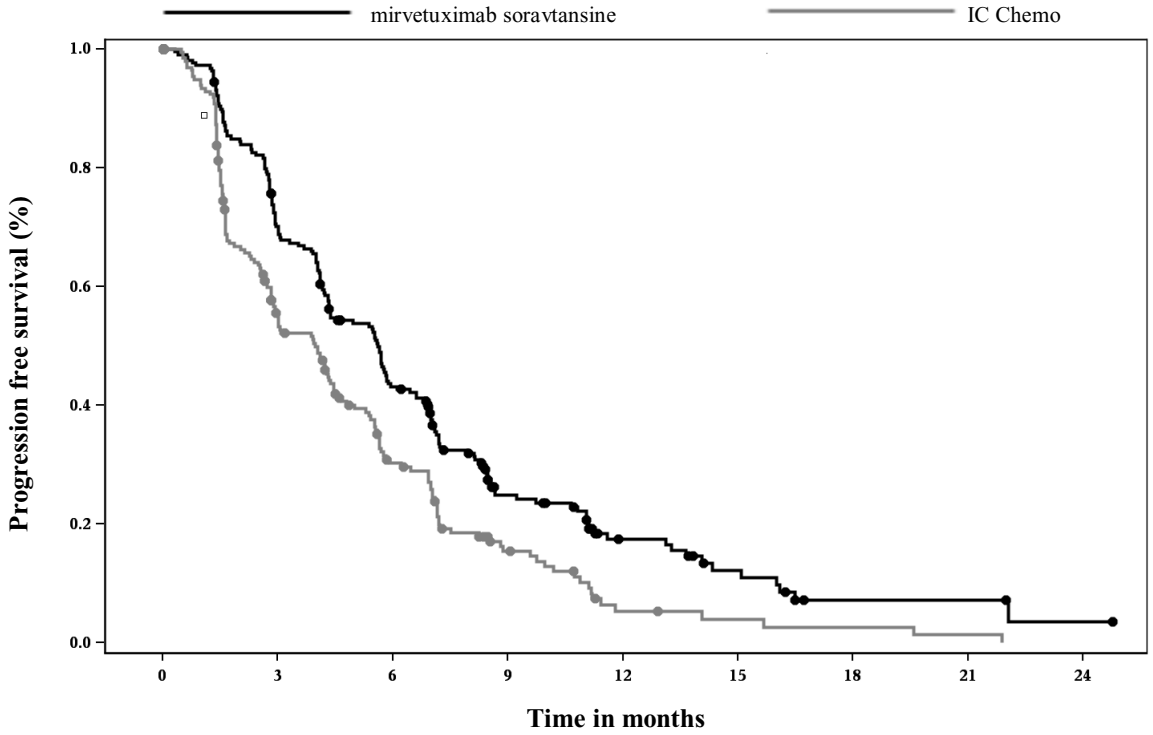
Efficacy parameter	ELAHERE N=227	IC chemotherapies N=226
Progression-free survival (PFS) as assessed by investigator		
Number of events (%)	176 (77.5)	166 (73.5)
Median, months (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Hazard ratio (95% CI)	0.65 (0.521, 0.808)	
p-value	<0.0001	
Overall survival (OS)		
Number of events (%)	90 (39.6)	114 (50.4)
Median, months (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Hazard ratio (95% CI)	0.67 (0.504, 0.885)	
p-value	0.0046*	

Data cut-off 06 March 2023.

*: pre-determined efficacy boundary = 0.01313, 2-sided (adjusted by observed number of deaths 204).

The Kaplan Meier curves for investigator-assessed PFS (median follow-up of 11.2 months) and OS (median follow-up of 13.1 months) are presented in Figure 1 and Figure 2.

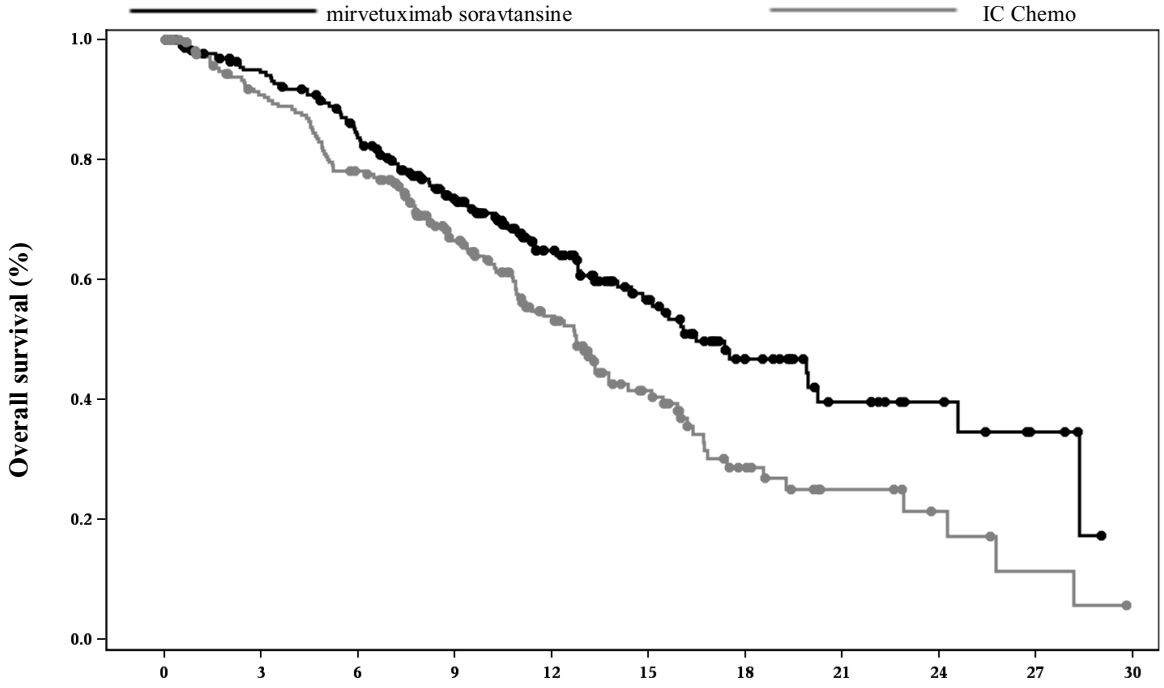
Figure 1: Kaplan-Meier curve for progression-free survival by treatment arm in MIRASOL (intent to treat population)



Number at risk

Mirvetuximab soravtansine	227	151	89	38	18	10	3	3	1
IC Chemo	226	98	48	19	5	3	2	1	0

Figure 2: Kaplan-Meier curve for overall survival by treatment arm in MIRASOL (intent to treat population)



Number at risk											
Mirvetuximab soravtansine	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

At an additional descriptive analysis with median follow-up of 20.3 months, OS results were consistent with the primary analysis.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ELAHERE in all subsets of the paediatric population in treatment of ovarian carcinoma, treatment of fallopian tube carcinoma, and treatment of peritoneal carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics were characterised after patients were administered mirvetuximab soravtansine 0.161 mg/kg to 8.71 mg/kg AIBW doses (i.e., 0.0268 times to 1.45 times the approved recommended dose of 6 mg/kg AIBW), unless otherwise noted.

Table 6 summarises the exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and its metabolite S-methyl-DM4 following administration after the first cycle (3-weeks) of mirvetuximab soravtansine 6 mg/kg to patients. Peak mirvetuximab soravtansine 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, and the peak S-methyl-DM4 concentrations were observed approximately 3 days after administration of mirvetuximab soravtansine. Steady state concentrations of mirvetuximab soravtansine, DM4, and S-methyl-DM4

were reached after 1 treatment cycle. Accumulation of the mirvetuximab soravtansine, DM4, and S-methyl-DM4 was minimal following repeat administration of mirvetuximab soravtansine.

Table 6: Exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 after first treatment cycle of 6 mg/kg of mirvetuximab soravtansine

	Mirvetuximab soravtansine Mean (±SD)	**Unconjugated DM4 Mean (±SD)**	**S-methyl-DM4 Mean (±SD)**
C_{max}	137.3 (±62.3) µg/mL	4.11 (±2.29) ng/mL	6.98 (±6.79) ng/mL
AUC_{tau}	20.65 (±6.84) h*mg/mL	530 (±245) h*ng/mL	1848 (±1585) h*ng/mL

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

Absorption

Mirvetuximab soravtansine is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

The mean (±SD) steady state volume of distribution of mirvetuximab soravtansine was 2.63 (±2.98) L. Human plasma protein binding of DM4 and S-methyl DM4 was >99%, *in vitro*.

Biotransformation

The monoclonal antibody portion of mirvetuximab soravtansine 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 AUCs, respectively.

Elimination

The mean (±SD) total plasma clearance of mirvetuximab soravtansine was 18.9 (±9.8) mL/hour. The mean terminal phase half-life of mirvetuximab soravtansine after the first dose was 4.9 days. For the unconjugated DM4, the mean (±SD) total plasma clearance was 14.5 (±4.5) mL/hour and the mean terminal phase half-life was 2.8 days. For S-methyl-DM4, the mean (±SD) total plasma clearance was 5.3 (±3.4) L/hour and the mean terminal phase half-life was 5.1 days. In vitro and nonclinical in vivo studies indicate that DM4 and S-methyl-DM4 are primarily metabolised by CYP3A4 and eliminated via biliary excretion in the faeces.

Special populations

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on age (32 to 89 years), race (White, Black, or Asian), body weight (36 to 136 kg), mild hepatic impairment (total bilirubin ≤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 mirvetuximab soravtansine 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

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.

5.3 Preclinical safety data

Target organs identified with single-dose administration of mirvetuximab soravtansine in cynomolgus monkeys were limited to skin and cellular depletion of the bone marrow and lymphoid tissue. Repeat dosing in cynomolgus monkeys and Dutch-belted rabbits also indicated ophthalmic findings including corneal microcysts, pigmentation, attenuation and degeneration/necrosis of the corneal epithelium. These findings were dose intensity (dose and schedule) dependent with fewer overall findings and recovery of those findings observed in the 3-week dosing schedule (the clinical dosing schedule).

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

DM4 and S-methyl DM4 were not mutagenic in the bacterial reverse mutation (Ames) assay. DM4 and S-methyl DM4 resulted in micronuclei in polychromatic erythrocytes.

No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine.

Fertility studies have not been conducted with mirvetuximab soravtansine or DM4. There are no data on the effect of ELAHERE on human fertility. However, given the mechanism of action of ELAHERE leads to microtubule disruption and death of rapidly dividing cells, there is the potential for drug-related fertility effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid (E260)
Sodium acetate (E262)
Sucrose
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

ELAHERE is incompatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

5 years

Diluted solution

After dilution the chemical and physical stability has been demonstrated between 1 mg/mL and 2 mg/mL for 8 hours at 15 ˚C – 25 ˚C or for 24 hours at 2 ˚C – 8 ˚C followed by 8 hours at 15 ˚C – 25 ˚C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store upright in a refrigerator (2 °C - 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminum seal with a royal blue polypropylene flip cap, containing 20 mL concentrate for solution.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

ELAHERE is a cytotoxic medicinal product. Follow applicable special handling and disposal procedures.

Preparation

- 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 section 4.2). 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 medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. ELAHERE is a clear to slightly opalescent, colourless solution.
- The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.
- 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 solution remaining in the vial.

Dilution

- ELAHERE must be diluted prior to administration with 5% glucose to a final concentration of 1 mg/mL to 2 mg/mL.
- ELAHERE is not compatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. ELAHERE must not be mixed with any other medicinal products or intravenous fluids.

- Determine the volume of 5% glucose required to achieve the final diluted active substance concentration. Either remove the excess 5% glucose from a pre-filled intravenous bag or add the calculated volume of 5% glucose to a sterile empty intravenous bag. Then add the calculated dose volume of ELAHERE to the intravenous bag.
- Gently mix the diluted 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 the solution in accordance with section 6.3. 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 the prepared infusion solution.

Administration

- Inspect the ELAHERE intravenous infusion bag visually for particulate matter and discolouration prior to administration.
- Administer pre-medications prior to ELAHERE administration (see section 4.2).
- 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.
- Use of administration delivery devices containing Di-2-ethylhexyl phthalate (DEHP) should be avoided.
- 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% glucose to ensure delivery of the full dose. Do not use any other intravenous fluids for flushing.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1866/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co KG
Birkendorfer Straβe 65
Biberach An Der Riβ, Baden-Württemberg, 88397, Germany

Name and address of the manufacturer responsible for batch release

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate,
Dundalk, A91 P9KD, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ELAHERE 5 mg/mL concentrate for solution for infusion
mirvetuximab soravtansine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL of concentrate for solution for infusion contains 5 mg mirvetuximab soravtansine. One vial contains 100 mg mirvetuximab soravtansine in 20 mL.

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid (E260), sodium acetate (E262), sucrose, polysorbate 20 (E432), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
100 mg/20 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic
Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1866/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ELAHERE 5 mg/mL sterile concentrate
mirvetuximab soravtansine
IV use after dilution

2. METHOD OF ADMINISTRATION

IV use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/20 mL

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ELAHERE 5 mg/mL concentrate for solution for infusion
mirvetuximab soravtansine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ELAHERE is and what it is used for

What ELAHERE is
ELAHERE is a cancer medicine that contains the active substance mirvetuximab soravtansine.

ELAHERE is used to treat adults with ovarian cancer, fallopian tube (one of two long, slender tubes that connect the ovaries to the womb) cancer, or primary peritoneal cancer (cancer that forms in the tissue that lines the abdominal wall and covers organs in the abdomen, and has not spread there from another part of the body). It is used in patients whose cancer cells have a protein on the surface known as folate receptor-alpha (FRα), and who have previously not responded to or are no longer responding to treatment with 'platinum-based' chemotherapy, and who have already received one to three prior treatments.

How ELAHERE works
The active substance in ELAHERE, mirvetuximab soravtansine, is made up of a monoclonal antibody which is attached to a cancer medicine. The monoclonal antibody is a protein that recognises and attaches to the FRα protein on the cancer cells. When this happens, mirvetuximab soravtansine enters the cancer cell and releases the cancer medicine DM4. DM4 then stops the normal growth process of the cancer cells. This can help kill cancer cells and stop the spread of the disease.

Your doctor will ensure that you have had a test confirming that you are eligible to receive ELAHERE. This test is done on tissue from your tumour. If you have tissue available from a previous surgery or biopsy, this archived material may be tested. If you do not have prior tissue, this test will require a tumour biopsy.

Talk to your doctor or nurse if you have any questions about how ELAHERE works or why this medicine has been prescribed for you.

2. What you need to know before you are given ELAHERE

You must not receive ELAHERE
- if you are allergic to mirvetuximab soravtansine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Before you are given ELAHERE, talk to your doctor or nurse if you:
- have vision or eye problems requiring active treatment or monitoring
- have nerve damage in the arms and legs; symptoms may include numbness, tingling, or weakness
- are pregnant or plan to become pregnant. ELAHERE could harm an unborn baby if taken during pregnancy.

Seek urgent medical attention if you have any of the following serious side effects (see section 4) during treatment:

- ***Eye problems.*** ELAHERE can cause severe eye problems such as loss of vision, damage to the cornea (the transparent layer in the front of the eye; keratopathy), dry eyes, abnormal sensitivity of the eyes to light (photophobia) or eye pain. You will see an eye specialist before starting treatment. It is important that you report any new or worsening eye problems before the start of each treatment cycle. It is recommended that you use drops to moisturise the eyes during treatment. If you develop certain side effects affecting the eyes, your doctor may recommend additional eye drops containing corticosteroids. You should not use contact lenses during treatment with ELAHERE unless advised by a healthcare professional. See 'Eye care' in section 3 for further information.
- ***Inflammation in the lungs.*** Severe, life-threatening scarring of the lungs (interstitial lung disease), including inflammation of the lungs can occur in patients treated with ELAHERE. Your doctor will monitor you for signs of lung inflammation. Tell your doctor if you develop coughing, wheezing, chest pain or difficulty breathing.
- ***Nerve damage in arms and legs.*** Nerve damage in arms and legs can be serious and severe and can occur when treated with ELAHERE. Your doctor will monitor you for signs of nerve damage. Tell your doctor if you develop symptoms of nerve damage such as sensations like numbness, tingling, pins and needles (paraesthesia), burning, pain, muscle weakness and distorted sense of touch (dysesthesia) in your arms or legs.
- ***Infusion-related reactions.*** Infusion-related reactions have occurred with ELAHERE. To minimise the risk of these reactions, your doctor will give you some medicines, see 'Medicines given before infusion' in section 3. In case of severe reactions, your doctor will stop the infusion immediately and you will be given supportive treatment.

If you experience any of the above-listed serious side effects, your doctor may withhold/reduce treatment until symptoms resolve, or in more serious cases, treatment will be permanently stopped.

Children and adolescents
This medicine must not be given to children or adolescents under 18 years because it has not been studied in this group.

Other medicines and ELAHERE
Tell your doctor if you are taking, have recently taken or might take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. This is because some medicines may affect the way ELAHERE works. Also, ELAHERE may affect the way other medicines work.

The following medicines may increase the risk of side effects of ELAHERE by increasing the amount of ELAHERE in the blood. These medicines include:
- ceritinib (cancer medicine to treat non-small cell lung cancer)
- clarithromycin (antibiotic for treating bacterial infections)

- cobicistat, ritonavir (antiviral medicines to treat HIV/AIDS)
- idelalisib (cancer medicine to treat certain blood cancers)
- itraconazole, ketoconazole, posaconazole, voriconazole (antifungal medicines to treat fungal infections)
- nefazodone (antidepressant)
- telithromycin (antibiotic for treating community acquired pneumonia)

Contraception
Women who could become pregnant must use an effective birth control (contraception) during treatment and for 7 months after the last dose of ELAHERE.

Pregnancy
ELAHERE could harm an unborn baby if taken during pregnancy because it contains a compound that can damage genes and cells that are growing rapidly. Therefore, using ELAHERE during pregnancy is not recommended. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you become pregnant during treatment with ELAHERE or within 7 months after stopping treatment, tell your doctor immediately.

If you are able to become pregnant, you will be asked to take a pregnancy test before you start treatment with ELAHERE.

Breast-feeding
Do not breast-feed during treatment and for 1 month after the last dose. ELAHERE may pass into breast milk.

Fertility
Fertility studies have not been conducted with ELAHERE and there are no data on the effect of the medicine on fertility. However, due to how the medicine works, fertility problems are possible when taking this medicine.

Driving and using machines
ELAHERE may affect your ability to drive and use machines. If you experience blurred vision, nerve damage causing pain, numbness or weakness in your hands, arms or feet, fatigue, or dizziness, do not drive, use tools, or operate machines until your symptoms are completely better.

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

ELAHERE contains polysorbate
This medicine contains 2.11 mg of polysorbate 20 in each vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How you will be given ELAHERE

ELAHERE will be given to you by a doctor or a nurse experienced in using cancer medicines.

Your doctor will calculate your dose based on your body weight. You will receive ELAHERE by an infusion (drip) into your vein (intravenously) over 2 to 4 hours, once every 3 weeks (this is known as a 21-day treatment cycle). Your doctor will decide how many cycles you need.

Medicines given before infusion

Your doctor will give you the following medicines about 30 minutes before each infusion:

- Corticosteroids (such as dexamethasone) to help prevent inflammation
- Antihistamines (such as diphenhydramine) to help prevent allergic reactions
- Antipyretics (such as paracetamol) to reduce fever

You may also be given corticosteroids the day before your infusion if you have previously suffered from infusion-related reactions.

Your doctor will also give you a medicine to reduce nausea and vomiting before each dose and thereafter as needed.

Eye care

An eye care specialist will examine your eyes prior to starting treatment with ELAHERE.

- Before each treatment cycle, it is important that you tell your doctor or eye care specialist if you have any new or worsening eye problems. If you develop moderate or severe eye problems during treatment, your doctor may reduce the dose of your treatment until your problems improve.
- Your doctor may adjust, withdraw or permanently stop ELAHERE treatment if signs and symptoms reveal any worsening problems in your eyes.

Contact lenses
- Do not wear contact lenses during treatment with ELAHERE, unless you are told to do so by your doctor or eye care specialist.

Eye drops
- You are recommended to use lubricating eye drops when needed throughout ELAHERE treatment.
- If you experience moderate or severe eye side effects, your doctor may recommend that you take topical steroid eye drops.
- It is important to follow your doctor's instruction for when to take steroid eye drops, and to wait at least 15 minutes after using the topical steroid eye drops before using the lubricating eye drops.

Changes to your dose if you suffer from side effects
Your doctor will adjust your dose of ELAHERE if you suffer from any side effects (see section 4, Possible side effects).

If you are given more ELAHERE than you should have been given
Since the infusion is given to you by your doctor or specialist nurse, an overdose is unlikely. If you inadvertently receive too much medicine, your doctor will take appropriate measures to monitor and support you.

If a dose of ELAHERE is missed
If you forget or miss your appointment, call your doctor or your treatment centre to make another appointment as soon as possible. Do not wait until your next planned visit. For the treatment to be fully effective, it is very important not to miss a dose unless recommended by your doctor.

If you stop treatment with ELAHERE
You should not stop treatment without talking with your doctor first.

The therapy with ELAHERE usually requires a number of treatment cycles. The number of infusions that you receive will depend on how your cancer is responding to treatment. Therefore, you should continue receiving ELAHERE even if you see your symptoms improve and until your doctor decides that ELAHERE should be stopped.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with this medicine.

Tell your doctor or nurse immediately or seek urgent medical attention if you experience any of the following side effects during or after treatment:

- ***Eye problems*** (very common – may affect more than 1 in 10 people): Signs or symptoms may include damage to the cornea, the transparent layer of the eye (keratopathy), clouding of the eye lens (cataract), blurred vision, sensitivity to light (photophobia), eye pain, and dry eye.
- ***Inflammation in the lungs*** (very common – may affect more than 1 in 10 people): Signs or symptoms may include difficulty breathing, cough, low levels of oxygen resulting in confusion, restlessness, rapid heart rate, bluish skin, or scarring of the lungs which would be picked up from an X-ray.
- ***Nerve damage in the arms and legs*** (very common – may affect more than 1 in 10 people): Signs and symptoms of nerve damage may include pins and needles sensation, tingling or a burning sensation, pain due to nerve damage, muscle weakness, and an unpleasant, abnormal sense of touch, particularly in your arms or legs.
- ***Infusion-related reactions / hypersensitivity*** (common – may affect up to 1 in 10 people): Signs and symptoms of infusion-related reactions may include low blood pressure, fever, chills, nausea, vomiting, headache, lightheadedness, difficulty breathing, wheezing, rash, flushing, swelling of the face or around the eye, sneezing, itchiness, muscle or joint pain.

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):

- urinary tract infection – UTI (infection of the parts of the body that collect and pass out urine)
- low red blood cell counts which can cause tiredness and pale skin (anaemia)
- low blood platelet counts which can lead to bleeding and bruising (thrombocytopenia)
- loss of appetite
- low blood magnesium levels, symptoms include nausea, weakness, twitching, cramping or irregular heart beat (hypomagnesaemia)
- headache
- swollen belly (abdominal distension)
- belly (abdominal) pain
- diarrhoea
- constipation
- feeling sick (nausea)
- vomiting
- joint pain (arthalgia)
- tiredness
- blood tests showing an increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in blood, indicating liver problems

Common (may affect up to 1 in 10 people):

- low levels of neutrophils, a type of white blood cell that fights infection (neutropenia)
- low blood potassium levels which can cause weakness, muscle cramps, tingling, and heart rhythm disturbance (hypokalaemia)
- dehydration
- difficulty falling and staying asleep, and poor quality of sleep (insomnia)
- taste disturbance (dysgeusia)
- feeling dizzy

- high blood pressure (hypertension)
- build-up of fluid in the abdomen (ascites)
- disease where stomach acid rises up into the food pipe (gastro-oesophageal reflux disease)
- inflammation of the lining of the mouth (stomatitis)
- indigestion (dyspepsia)
- high blood bilirubin levels (hyperbilirubinemia) which may cause yellowing of skin or eyes
- itching (pruritis)
- muscle pain (myalgia)
- back pain
- pain in arms, hands, legs and feet
- muscle spasms
- blood tests showing an increase in alkaline phosphatase (ALP) levels and gamma-glutamyl transferase (GGT) levels in the blood, indicating liver problems
- weight loss

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store ELAHERE

ELAHERE will be stored by the doctor and pharmacist at the hospital or clinic.

The following information is intended for healthcare professionals

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store the vials upright in a refrigerator (2 °C - 8 °C). Do not freeze.

Keep the vial in the outer carton in order to protect it from light.

If the diluted infusion solution is not used immediately, store it either at room temperature (15 °C - 25 °C) for no more than 8 hours (including infusion time), or in a fridge (2 °C - 8 °C) for no more than 24 hours followed by room temperature (15 °C - 25 °C) for no more than 8 hours (including infusion time).

Do not use this medicine if you notice the solution is cloudy or discoloured.

Do not throw away any medicines via wastewater. The hospital pharmacist will throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ELAHERE contains
- The active substance is mirvetuximab soravtansine.
- The other ingredients are glacial acetic acid (E260), sodium acetate (E262), sucrose, polysorbate 20 (E432), and water for injections (see section 2).

What ELAHERE looks like and contents of the pack
The medicine is a clear to slightly opalescent, colourless solution. It comes in a glass vial with a rubber stopper, an aluminium seal and royal blue flip cap.

Each pack contains 1 vial.

Marketing Authorisation Holder
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

Manufacturer
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate,
Dundalk, A91 P9KD, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
AbbVie SA
Tél/Tel: +32 10 477811

България
АбВи ЕООД
Тел: +359 2 90 30 430

Česká republika
AbbVie s.r.o.
Tel: +420 233 098 111

Danmark
AbbVie A/S
Tlf: +45 72 30-20-28

Deutschland
AbbVie Deutschland GmbH & Co. KG
Tel: 00800 222843 33 (gebührenfrei)
Tel: +49 (0) 611 / 1720-0

Eesti
AbbVie OÜ
Tel: +372 623 1011

Ελλάδα
AbbVie ΦΑΡΜΑΚΕΥΤΙΚΗ Α.Ε.
Τηλ: +30 214 4165 555

España
AbbVie Spain, S.L.U.
Tel: +34 91 384 09 10

Lietuva
AbbVie UAB
Tel: +370 5 205 3023

Luxembourg/Luxemburg
AbbVie SA
Belgique/Belgien
Tél/Tel: +32 10 477811

Magyarország
AbbVie Kft.
Tel: +36 1 455 8600

Malta
V.J.Salomone Pharma Limited
Tel: +356 21220174

Nederland
AbbVie B.V.
Tel: +31 (0)88 322 2843

Norge
AbbVie AS
Tlf: +47 67 81 80 00

Österreich
AbbVie GmbH
Tel: +43 1 20589-0

Polska
Abbvie Sp. z o.o.
Tel: +48 22 372 78 00

France
AbbVie
Tél: +33 (0) 1 45 60 13 00

Hrvatska
AbbVie d.o.o.
Tel: +385 (0)1 5625 501

Ireland
AbbVie Limited
Tel: +353 (0)1 4287900

Ísland
Vistor hf.
Tel: +354 535 7000

Italia
AbbVie S.r.l.
Tel: +39 06 928921

Κύπρος
Lifepharma (Z.A.M.) Ltd
Τηλ: +357 22 34 74 40

Latvija
AbbVie SIA
Tel: +371 67605000

Portugal
AbbVie, Lda.
Tel: +351 (0)21 1908400

România
AbbVie S.R.L.
Tel: +40 21 529 30 35

Slovenija
AbbVie Biofarmacevtska družba d.o.o.
Tel: +386 (1)32 08 060

Slovenská republika
AbbVie s.r.o.
Tel: +421 2 5050 0777

Suomi/Finland
AbbVie Oy
Puh/Tel: +358 (0)10 2411 200

Sverige
AbbVie AB
Tel: +46 (0)8 684 44 600

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Other sources of information

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

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

The following information is intended for healthcare professionals only:

ELAHERE is a cytotoxic medicinal product. Follow applicable special handling and disposal procedures.

Preparation

- Calculate the dose (mg) (based on the patient's adjusted ideal body weight (AIBW)), total volume (mL) of solution required, and the number of vials of ELAHERE needed. 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 medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. ELAHERE is a clear to slightly opalescent, colourless solution.
- The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

- 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 solution remaining in the vial.

Dilution
- ELAHERE must be diluted prior to administration with 5% glucose to a final concentration of 1 mg/mL to 2 mg/mL.
- ELAHERE is not compatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. ELAHERE must not be mixed with any other medicinal products or intravenous fluids.
- Determine the volume of 5% glucose required to achieve the final diluted active substance concentration. Either remove the excess 5% glucose from a prefilled intravenous bag or add the calculated volume of 5% glucose to a sterile empty intravenous bag. Then add the calculated dose volume of ELAHERE to the intravenous bag.
- Gently mix the diluted solution by slowly inverting the bag several times to assure uniform mixing. Do not shake or agitate.
- After dilution the chemical and physical stability has been demonstrated between 1 mg/mL and 2 mg/mL for 8 hours at 15 ˚C – 25 ˚C or for 24 hours at 2 ˚C – 8 ˚C followed by 8 hours at 15 ˚C – 25 ˚C.
- From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.
- If the diluted infusion solution is not used immediately, store the solution in accordance with section 6.3 of the Summary of the Product Characteristics. 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 the prepared infusion solution.

Administration
- Inspect the ELAHERE intravenous infusion bag visually for particulate matter and discolouration prior to administration.
- Administer pre-medications prior to ELAHERE administration (see section 4.2).
- 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.
- Use of administration delivery devices containing di-2-ethylhexyl phthalate (DEHP) should be avoided.
- 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% glucose to ensure delivery of the full dose. Do not use any other intravenous fluids for flushing.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.