swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ELAHERE

International non-proprietary name:	mirvetuximab soravtansine
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	100 mg/20 mL
Route(s) of administration:	intravenous
Marketing authorisation holder:	AbbVie AG
Marketing authorisation no.:	69700
Decision and decision date:	approved on 13 March 2025

Note:

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

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

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

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

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 19 January 2024.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

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 "Dosage/Administration", section "Properties/Effects – Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Before each ELAHERE infusion: pre-treatment with corticosteroid, antihistamine, antipyretic, and antiemetic.
ELAHERE: 6 mg/kg adjusted ideal body weight (AIBW) once every 3 weeks as an i.v. infusion.
In case of toxicity: reduce to 5 mg/kg AIBW or 4 mg/kg AIBW. If a dose of 4 mg/kg AIBW still causes unacceptable toxicity, stop treatment permanently.

AIBW = ideal body weight (IBW [kg]) + 0.4*(actual body weight [kg] – IBW)
IBW [kg] for women = 0.9*height [cm] – 92

For a patient whose height is 165 cm and actual weight is 80 kg:

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 November 2024
Formal control completed	5 November 2024
Preliminary decision	14 January 2025
Response to preliminary decision	14 February 2025
Labelling corrections and/or other aspects	28 February 2025
Response to labelling corrections and/or other aspects	5 March 2025
Final decision	13 March.2025
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the publicly available assessment report Elahere, Procedure No EMEA/H/C/005036/0000 issued by EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Elahere, Procedure No EMEA/H/C/005036/0000 issued by EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Elahere, Procedure No EMEA/H/C/005036/0000 issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Elahere, Procedure No EMEA/H/C/005036/0000 issued by the EMA.

6 Risk management plan summary

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

7 Appendix

Approved Information for healthcare professionals

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

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

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

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

ELAHERE

Composition

Active substances

Mirvetuximab *s*oravtansine (produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology).

Excipients

Acetic acid, glacial, polysorbate 20, sodium acetate anhydrous (corresponding to 2.94 mg sodium per vial), sucrose, water for injection.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion

One vial contains 100 mg mirvetuximab soravtansine in 20 mL (5 mg/ml).
Clear to slightly opalescent, colourless solution.

Indications/Uses

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 "Dosage/Administration", section "Properties/Effects – Clinical efficacy").

Dosage/Administration

ELAHERE must be initiated and supervised by a physician experienced in the use of anticancer medicinal products.
In order to ensure the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patient selection

Eligible patients should have FR*α* 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	paracetamol 325 mg to 650 mg	
Antiemetic	oral or intravenous	5-hydroxytryptamine 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. Patients who experience ocular adverse reactions should have a complete ophthalmic exam at the emergence of symptoms, at least every other cycle thereafter and as clinically indicated, until resolution, stabilization or return to baseline of the adverse reactions.

Ophthalmic topical steroids

The use of ophthalmic topical steroids is recommended, unless the patient's ophthalmologist decides that the risks outweigh the benefits of such therapy. 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 section "Warnings and precautions").

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 sections "Warnings and precautions").

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.
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 “Warnings and precautions” and “Undesirable effects”)	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.
Uveitis (see sections “Warnings and precautions” and “Undesirable effects”)	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	Grade 1	Monitor.

Adverse reaction	Severity of adverse reaction*	Dose modification
(see sections “Warnings and precautions” and “Undesirable effects”)	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.
	Grade 3 or 4	Permanently discontinue.
Peripheral neuropathy (see sections “Warnings and precautions” and “Undesirable effects”)	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 “Warnings and precautions” and “Undesirable effects”)	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 “Undesirable effects”)	Grade 3 or 4	Withhold dose until Grade 1 or less, then resume at one lower dose level.
Other adverse reactions (see section “Undesirable effects”)	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

ELAHERE is not approved for use in the paediatric population.

Elderly patients

Of the 682 patients with epithelial ovarian cancer who were treated with ELAHERE across studies, 44 % of patients were ≥65 years old. No dose adjustment of ELAHERE is recommended in patients ≥ 65 years of age (see section “Pharmacokinetics”).

Patients with renal disorders

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 “Pharmacokinetics”).

Patients with hepatic disorders

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 “Pharmacokinetics”).
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.
ELAHERE must not be mixed with other medicines.
Instructions for reconstitution of the medicinal product before use, see section “Preparation” and section “Dilution”.

Contraindications

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

Warnings and precautions

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 “Effects on ability to drive and use machines” and “Undesirable effects”).
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 “Dosage/Administration”).
It is recommended to use premedication with lubricating eye drops and opthalmic topical steroids during treatment with mirvetuximab soravtansine (see section “Dosage/Administration”).
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 “Dosage/Administration”).
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 “Undesirable effects”).
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 “Dosage/Administration”). Patients who are asymptomatic may continue dosing of mirvetuximab soravtansine with close monitoring.

Peripheral neuropathy

Peripheral neuropathy has occurred with mirvetuximab soravtansine, including Grade ≥3 reactions (see section “Undesirable effects”).
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 “Dosage/Administration”).

Embryo-fetal toxicity

Based on its mechanism of action, mirvetuximab soravtansine could cause embryo-fetal 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 “Pregnancy, lactation”).

Excipients with known effect

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

Interactions

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 “Pharmacokinetics”), which may increase the risk of ELAHERE adverse reactions (see section “Undesirable effects”). If concomitant use with strong CYP3A4 inhibitors (e.g. ceritinib, clarithromycin, cobicistat, idelalisib, itraconazole, ketoconazole, posaconazole, ritonavir, 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.

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

Pregnancy, lactation

Women of childbearing potential/Contraception

Women of childbearing age should have their pregnancy status checked before starting treatment with mirvetuximab soravtansine. During the treatment and for 7 months after the last use of mirvetuximab soravtansine a reliable method of contraception should be used.

Pregnancy

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

Effects on 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.

Undesirable effects

Summary of the safety profile

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) 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 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 adverse effects are listed according to MedDRA system organ class and organized according to the following convention: 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 (10%)
Blood and lymphatic system disorders	Very common	Anaemia (12%), thrombocytopenia (10%)
	Common	Neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite (22%), hypomagnesaemia (11%)
	Common	Hypokalaemia, dehydration
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Peripheral neuropathy[1] (36%), headache 19%

System Organ Class	Frequency category	Adverse reactions
	Common	Dysgeusia, dizziness
Eye disorders	Very common	Keratopathy[2] (36%), cataract[3] (16%), blurred vision event[4] (48%), photophobia (14%), eye pain (10%), dry eye[5] (27%)
	Common	Ocular discomfort[6]
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Pneumonitis[7] (10%) dyspnoea (12%), cough (12%)
Gastrointestinal disorders	Very common	Diarrhoea (39%), abdominal pain[8] (37%) constipation (26%), abdominal distension (10%), vomiting (23%), nausea (41%)
	Common	Ascites, gastro-oesophageal reflux disease, stomatitis, dyspepsia
Hepatobiliary disorders	Very common	Aspartate aminotransferase increased (16%), alanine aminotransferase increased (13%)
	Common	Hyperbilirubinaemia, blood alkaline phosphatase increased, gamma-glutamyl transferase increased
Skin and subcutaneous tissue disorders	Common	Pruritus
Musculoskeletal and connective tissue disorders	Very common	Arthralgia (16%), Myalgia (10%), back pain (10%)
	Common	Pain in extremity, muscle spasms
General disorders and administration site conditions	Very common	Fatigue (35 %)
	Common	Pyrexia, weight decreased
Injury, poisoning and procedural complication	Common	Infusion related reaction/hypersensitivity[9]

[1] Peripheral neuropathy includes hypoaesthesia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy (see section “Description of specific adverse reactions and additional information”).
[2] Keratopathy 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 specific adverse reactions and additional information”).
[3] Cataract includes cataract, cataract cortical, and cataract nuclear (see section “Description of specific adverse reactions and additional information”).
[4] Blurred vision event includes accommodation disorder, diplopia, hypermetropia, presbyopia, refraction disorder, vision blurred, visual impairment, visual acuity reduced, and vitreous floaters (see section “Description of specific adverse reactions and additional information”).
[5] Dry eye includes dry eye and lacrimation decreased (see section “Description of specific adverse reactions and additional information”).
[6] Ocular discomfort includes eye irritation, eye pruritus, foreign body sensation in eye, and ocular discomfort (see section “Description of specific adverse reactions and additional information”).
[7] Pneumonitis includes interstitial lung disease, organising pneumonia, pneumonitis, pulmonary fibrosis, and respiratory failure (see section “Description of specific adverse reactions and additional information”).
[8] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.
[9] Infusion related reaction/hypersensitivity includes SMQ Hypersensitivity narrow and flushing, erythema, erythema of eyelid.

Description of specific adverse reactions and additional information

Ocular disorders

Ocular adverse reactions (grouped terms) occurred in 59 % (405/682) of patients with EOC treated with mirvetuximab soravtansine. The most common (≥5 %) ocular adverse reactions were blurred vision (48 %), keratopathy (36 %), dry eye (27 %), cataract (16 %), photophobia (14 %), and eye pain (10 %). 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. Peripheral neuropathy adverse events included peripheral neuropathy (20 %), peripheral sensory neuropathy (9 %), paresthesia (6 %), neurotoxicity (3 %), hypoesthesia (1 %), peripheral motor neuropathy (0.9 %), polyneuropathy (0.3 %), and peripheral sensorimotor neuropathy (0.1 %) 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.

Immunogenicity

The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the test. In addition, the observed incidence of antibody positivity (including neutralizing antibodies) can be influenced by several factors in a test, such as test methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For this reason, the comparison of the incidence of antibodies against mirvetuximab soravtansine from the studies described with the incidence of antibodies against mirvetuximab soravtansine from other studies may be misleading.
In studies *IMGN853*-0416, 0417, 0401, and 0403 in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who received ELAHERE at 6 mg/kg AIBW administered intravenously once every 3 weeks, 9 % (57/626) developed anti-drug antibodies. Neutralizing antibodies were detected in 47 % (27/57) of patients who were ADA-positive.
No clinically meaningful difference was observed in the trough concentrations of mirvetuximab soravtansine between ADA-positive and ADA-negative patients. Anti-mirvetuximab soravtansine antibody formation was associated with a higher incidence of infusion-related reactions. The effect of anti-drug antibodies on effectiveness has not been fully characterized. Based on limited data, the presence of anti-mirvetuximab soravtansine antibodies may be associated with decreased efficacy in ADA-positive patients when compared to ADA-negative patients.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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.

Properties/Effects

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.

Pharmacodynamics

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

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 VENTANA 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 ECOG³2 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).

Pharmacokinetics

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*.

Metabolism

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.

Kinetics in specific patient groups

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.

Preclinical 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.

Other information

Incompatibilities

ELAHERE is incompatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. The medicinal product may only be mixed with the medicinal products listed under instructions for handling.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
The preparation contains no preservative. After dilution between 1.0 mg/ml and 2.0 mg/ml, chemical and physical in-use stability was demonstrated 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, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store upright in a refrigerator (2 °C - 8 °C).
Do not freeze.
Do not shake.
Keep the vial in the outer carton in order to protect from light.
Keep out of the reach of children.

Instructions for 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 “Dosage/Administration”). 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 discoloration 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 “shelf life”. 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 discoloration prior to administration.
- Administer pre-medications prior to ELAHERE administration (see section “Dosage/Administration”).
- 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.

Authorisation number

69700 (Swissmedic)

Packs

Package with 1 vial of 100mg/20 ml [A].

Marketing authorisation holder

AbbVie AG, 6330 Cham

Date of revision of the text

January 2025