swissmedic

Date: 14 January 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Hetronifly

International non-proprietary name: serplulimab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 100 mg/10 mL
Route(s) of administration: intravenous
Marketing authorisation holder: Accord Healthcare AG
Marketing authorisation no.: 69906
Decision and decision date: approved on 27 November 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.

Table of contents

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
EMA	European Medicines Agency
ERA	Environmental risk assessment
ES-SCLC	Extensive-stage small cell lung cancer
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human 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
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
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) and information regarding procedure

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

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 6 September 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

Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2.2.2 Approved indication

Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 4.5 mg/kg serplulimab every 3 weeks until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	1 November 2024
Formal objection	29 November 2024
Response to formal objection	19 January 2025
Formal control completed	24 January 2025
Preliminary decision	21 May 2025
Response to preliminary decision	10 August 2025
Labelling corrections and/or other aspects	31 October 2025
Response to labelling corrections and/or other aspects	10 November 2025
Final decision	27 November 2025
Decision	approval

Based on Art. 13 TPA, 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 assessment report for Hetronifly EMA/48095/2025 dated 11 February 2025 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 EMA (see section 2.3 Regulatory history (milestones).

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 EMA (see section 2.3 Regulatory history (milestones))

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 EMA (see section 2.3 Regulatory history (milestones).

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 Hetronifly 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.

HETRONIFLY®

Composition

Active substances

Serplulimab (produced using genetic engineering with CHO [Chinese hamster ovary] cells).

Excipients

Citric acid monohydrate (E330), sodium citrate dihydrate (E331), mannitol (E421), sodium chloride, polysorbate 80 (E433), water for injections.
Each 10 ml vial contains 22.5 mg sodium.

Pharmaceutical form and active substance quantity per unit

HETRONIFLY 10 mg/ml concentrate for solution for infusion (i.v.). One vial of 10 ml of concentrate contains 100 mg of serplulimab (concentration 10 mg/ml).
Serplulimab is a humanised antibody (IgG4/kappa isotype with a stabilising sequence alteration in the hinge region) produced in Chinese hamster ovary cells by recombinant DNA technology.

Indications/Uses

HETRONIFLY in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Dosage/Administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Posology

The recommended dose is 4.5 mg/kg bodyweight serplulimab every 3 weeks until disease progression or unacceptable toxicity.

Dose delay or discontinuation (see also "Warnings and precautions")

Dose escalation or reduction of HETRONIFLY is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. Dose withholding for up to 12 weeks for tolerability is acceptable (see "Warnings and precautions").

Recommended management of immune-mediated adverse reactions are described in Table 1.

Table 1. Recommended treatment modifications

Adverse reactions	**Severity**	**Treatment modification[#]**
Immune-mediated lung disease	Grade 2	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grade 2 or 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Immune-mediated hepatitis	Grade 2 with AST or ALT > 3 to 5 times ULN, or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 with AST or ALT > 5 times ULN, or total bilirubin > 3 times ULN[†]	Permanently discontinue
Immune-mediated nephritis and renal insufficiency	Grade 2 elevation of serum creatinine	Withhold until adverse reactions recover or improve to Grade 1

Adverse reactions	Severity	Treatment modification[#]
	Grade 3 or 4 elevation of serum creatinine	Permanently discontinue
Immune-mediated endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis, Grade 2 adrenal insufficiency, Grade 3 hyperglycaemia or type 1 diabetes mellitus	Withhold until symptoms resolve and management with corticosteroids is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 hyperglycaemia	Permanently discontinue
Immune-mediated skin reactions	Grade 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-mediated adverse reactions	Grade 3 or 4 elevation of serum amylase or lipase Grade 2 or 3 pancreatitis Grade 2 myocarditis* Grade 2 or 3 other immune-mediated adverse reactions that have occurred for the first time	Withhold until adverse reactions recover or improve to Grade 1

Adverse reactions	Severity	Treatment modification[#]
	Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	
	Grade 4 pancreatitis or recurrent pancreatitis of any grade Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 4 other immune-mediated adverse reactions that have occurred for the first time Grade 4 or recurrent Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Permanently discontinue
Infusion-related reactions	Grade 2	Reduce infusion rate to half rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).

#: Serplulimab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with hormone replacement (see “Warnings and precautions” and “Undesirable effects”).

†: ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

*: The safety of retreatment with serplulimab in patients who experienced immune-mediated myocarditis is not clear.

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is needed for patients with mild (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST) hepatic impairment. There are insufficient data in patients with moderate (bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment and no data are available in severe (bilirubin > 3 × ULN and any AST) hepatic impairment. No dose recommendation can be made for patients with moderate or severe hepatic impairment (see “Pharmacokinetics”).

Patients with renal disorders

No dose adjustment is needed for patients with mild (CRCL=60-89 ml/min) or moderate (CRCL=30-59 ml/min) renal impairment. There are insufficient data and no dose recommendation can be made in patients with severe (CRCL=15-29 ml/min) renal impairment (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is needed for elderly patients (≥ 65 years) (see “Pharmacodynamics“ and Pharmacokinetics”).

Children and adolescents

HETRONIFLY is not approved for use in the pediatric population.

Method of administration

HETRONIFLY is for intravenous use.
The initial infusion rate should be set up to 100 ml per hour. If the first infusion is well tolerated, all subsequent infusions may be shortened to 30 minutes (± 10 minutes).
When administered in combination with chemotherapy, HETRONIFLY should be given first followed by chemotherapy on the same day. Use separate infusion bags for each infusion.
HETRONIFLY must not be administered as an intravenous push or bolus injection.
The total dose of HETRONIFLY required should be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection (see “Instructions for handling”).
For instructions on dilution and handling of the medicinal product before administration, see “Instructions for handling”.

Contraindications

Hypersensitivity to active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving serplulimab (see “Undesirable effects”). Most immune-mediated adverse reactions occurring during treatment were reversible and managed by withholding treatment, administration of corticosteroids, and/or supportive care (see “Dosage/Administration”). Immune-mediated adverse reactions have also occurred up to 3.6 months after the last dose. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.
For suspected immune-mediated adverse reactions, adequate evaluation to confirm the aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, treatment should be withheld, and corticosteroids administered. For most Grade 2 and some specific Grade 3 or 4 immune-mediated adverse reactions, administration should be withheld until recovery or improvement to Grade 1. Serplulimab must be permanently discontinued for any Grade 4 and some specific Grade 3 immune-mediated adverse reactions. For Grade 3, 4 and some specific Grade 2 immune-mediated adverse reactions (e.g., immune-mediated pneumonitis, immune-mediated myocarditis), corticosteroids (1-2 mg/kg/day prednisone or equivalent) and other symptomatic treatments should be given according to the clinical symptoms until recovery or improvement to Grade 1. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy (e.g., infliximab) should be added if there is worsening or no improvement despite corticosteroid use.

Immune-mediated pneumonitis

Immune-mediated pneumonitis, including fatal cases, has been reported in patients receiving HETRONIFLY (see “Undesirable effects”). Patients should be monitored for signs and symptoms of immune-mediated pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Suspected immune-mediated pneumonitis should be confirmed with radiographic imaging to exclude other causes. For treatment modification, see “Dosage/Administration”.

Immune-mediated colitis

Immune-mediated colitis, including fatal cases, has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for signs and symptoms of immune-mediated colitis, such as abdominal pain, diarrhoea, mucus, or blood in stool. Infection and other

disease-mediated aetiologies should be ruled out. For treatment modification, see “Dosage/Administration”. The potential risk of gastrointestinal perforation should be taken into consideration and confirmed by radiographic imaging and/or endoscopy if necessary.

Immune-mediated hepatitis

Immune-mediated hepatitis, including fatal cases, has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored periodically (every month) for changes in liver function and clinical signs and symptoms of immune-mediated hepatitis such as transaminase and total bilirubin elevations. Infection and diseases-related aetiologies should be ruled out. The frequency of liver function test should be increased, if immune-mediated hepatitis occurs. For treatment modification, see “Dosage/Administration”.

Immune-mediated nephritis and renal insufficiency

Immune-mediated nephritis and renal insufficiency has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored periodically (every month) for changes in renal function and clinical signs and symptoms of immune-mediated nephritis and renal insufficiency. The frequency of renal function tests should be increased, if immune-mediated nephritis occurs. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out. For treatment modification, see “Dosage/Administration”.

Immune-mediated endocrinopathies

Thyroid diseases

Thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis, have been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for changes in thyroid function and clinical signs and symptoms of thyroid disorders. For Grade 2 or 3 symptomatic hypothyroidism, serplulimab should be withheld and thyroid hormone replacement should be initiated as needed. For Grade 2 or 3 symptomatic hyperthyroidism, serplulimab should be withheld and anti-thyroid medicinal product should be initiated as needed. If acute inflammation of the thyroid is suspected, serplulimab should be withheld and initiate hormone therapy. Treatment may be resumed when symptoms of hypothyroidism or hyperthyroidism are controlled, and thyroid function is improved. For life-threatening hyperthyroidism or hypothyroidism, serplulimab must be permanently discontinued. Thyroid function should be monitored continuously to ensure appropriate hormone replacement (see “Dosage/Administration”).

Pituitary disorders

Hypophysitis has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for signs and symptoms of hypophysitis, and other causes should be ruled out. For Grade 2 or 3 symptomatic hypophysitis, serplulimab should be withheld, and hormone replacement should be initiated as needed. If acute hypophysitis is suspected, corticosteroids should be initiated. For life-threatening Grade 4 hypophysitis, serplulimab must be permanently discontinued (see “Dosage/Administration”).

Adrenal insufficiency

Adrenal insufficiency has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for signs and symptoms, and other causes should be ruled out. For Grade 2 adrenal insufficiency, serplulimab should be withheld and hormone replacement should be initiated as needed. For life-threatening Grade 3 or 4 adrenal insufficiency, serplulimab must be permanently discontinued. Adrenal gland function and hormone levels should be monitored continuously to ensure appropriate hormone replacement (see “Dosage/Administration”).

Hyperglycaemia

Hyperglycaemia or type 1 diabetes mellitus has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for blood glucose level and related clinical signs and symptoms. Insulin replacement therapy should be initiated as needed. For type 1 diabetes mellitus with poor blood glucose control, serplulimab should be withheld, and insulin replacement therapy should be initiated until the symptoms are improved. For life-threatening Grade 4 type 1 diabetes mellitus, serplulimab must be permanently discontinued. Blood glucose levels should be monitored continuously to ensure appropriate insulin replacement (see “Dosage/Administration”).

Immune-mediated skin reactions

Immune-mediated skin reactions have been reported in patients receiving serplulimab (see “Undesirable effects”). For Grade 1 or 2 rash, serplulimab can be continued, and symptomatic treatment or local corticosteroids treatment can be given. For Grade 3 rash, serplulimab should be withheld, and symptomatic treatment or local corticosteroids treatment should be given. For Grade 4 rash, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN), serplulimab should be permanently discontinued (see “Dosage/Administration”).

Immune-mediated pancreatitis

Immune-mediated pancreatitis, including increases in serum amylase and lipase levels and fatal cases, has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for changes in serum lipase and amylase (at the beginning of treatment, periodically during treatment, and as indicated based on clinical evaluation), and clinical signs and symptoms of pancreatitis. Serplulimab should be withheld for Grade 3 or 4 increase in serum amylase or lipase levels, and Grade 2 or 3 pancreatitis. For Grade 4 pancreatitis or recurrent pancreatitis of any grade, serplulimab should be permanently discontinued (see “Dosage/Administration”).

Immune-mediated myocarditis

Immune-mediated myocarditis, including fatal cases, has been reported in patients receiving serplulimab (see “Undesirable effects”). Patients should be monitored for clinical signs and symptoms of myocarditis. Suspected immune-mediated myocarditis should be confirmed with myocardial enzyme examinations, and other causes excluded. For Grade 2 myocarditis, serplulimab should be withheld, and corticosteroid treatment should be given. The safety of restarting serplulimab treatment in patients previously experiencing immune-mediated myocarditis is unclear. A multidisciplinary discussion is recommended before restarting serplulimab in patients with previous Grade 2 myocarditis, and the decision should be based on various clinical factors, including the degree of cardiac recovery, oncological response to the treatment, availability of alternative oncology treatments and prognosis. For Grade 3 or 4 myocarditis, serplulimab must be permanently discontinued and corticosteroids therapy should be initiated. Once a diagnosis of myocarditis is established, serplulimab should be withheld or permanently discontinued. Myocardial enzymes and cardiac function should be monitored closely for any grade myocarditis (see “Dosage/Administration”).

Immune-mediated uveitis

If uveitis and other immune-mediated adverse reactions occur at the same time, such as Vogt-Koyanagi-Harada syndrome, systemic corticosteroids should be given to prevent permanent blindness.

Other immune-mediated adverse reactions

Given the mechanism of action of serplulimab, other potential immune-mediated adverse reactions may occur. Other fatal and life-threatening immune-mediated adverse reactions have been observed in patients treated with serplulimab in clinical trials across doses and tumour types: thrombocytopenia, acute coronary syndrome, myocardial infarction and immune-mediated encephalitis (see “Undesirable effects”).

For other suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology and exclude other causes. Based on the severity of adverse reactions, serplulimab should be withheld for Grade 2 or 3 immune-mediated adverse reactions which occur for the first time. For recurrent Grade 3 immune-mediated adverse reactions (except endocrinopathies) and Grade 4 immune-mediated adverse reactions, serplulimab must be permanently discontinued. Corticosteroids can be initiated as clinically indicated (see “Dosage/Administration”).

Infusion-related reactions

Infusion-related reactions have been reported in patients receiving serplulimab. Patients should be monitored for clinical signs and symptoms of infusion-related reactions. Patients with Grade 1 infusion-related reactions may continue administration under close monitoring. The rate of infusion should be reduced, or treatment should be interrupted in patients with Grade 2 infusion-related reactions. Antipyretic and antihistamines may be considered. Treatment with serplulimab may be resumed under close monitoring when Grade 2 infusion-related reactions are controlled. For Grade ≥ 3 infusion-related reactions, infusion should be stopped immediately, treatment should be permanently discontinued, and appropriate treatment should be given (see “Dosage/Administration”).

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: a history of active or prior documented autoimmune disease, patients with active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 28 days prior to serplulimab administration, patients with any active infection requiring systemic anti-infective therapy within 14 days prior to the first dose, history of pneumonitis or interstitial lung disease, patients with active brain metastases, history of significant cardiovascular disease (e.g. myocardial infarction within half a year), a history of hypersensitivity to another monoclonal antibody, systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab.

Sodium

This medicinal product contains 22.5 mg of sodium per 10 ml vial, equivalent to 1.1% of the maximum daily sodium intake for an adult recommended by the WHO, which is 2 g from dietary sources.

Patient card

The prescriber must discuss the risks of serplulimab therapy with the patient. The patient will be provided with the patient card with each prescription.

Interactions

Drug-drug interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition, or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of serplulimab.
The use of systemic corticosteroids or immunosuppressants before starting serplulimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-mediated adverse reactions after starting serplulimab (see “Warnings and precautions”).

Pregnancy, lactation

Women of childbearing potential/contraception

Women of childbearing potential should use effective contraception during treatment and for at least 6 months after the last dose of serplulimab.

Pregnancy

There is no data on the use of serplulimab in pregnant women. Animal studies have demonstrated that inhibition of the PD-1 pathway causes embryofoetal toxicity (see “Preclinical data”). Human IgG is known to cross the placental barrier and serplulimab is an IgG4; therefore, it has the potential to be transmitted from the mother to the developing foetus. Serplulimab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether serplulimab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, whereby concentrations can drop to a low level; consequently, a risk to the breast-fed infant cannot be excluded during this period. Afterwards, serplulimab could be used during breast-feeding if clinically needed.

Fertility

Studies to evaluate fertility have not been performed. Thus, the effect of serplulimab on male and female fertility is unknown.

Effects on ability to drive and use machines

Serplulimab has minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see “Undesirable effects”), patients should be advised to use caution when driving or operating machinery until they are certain that serplulimab does not adversely affect them.

Undesirable effects

Summary of the safety profile

The safety of serplulimab in combination with chemotherapy is based on data in 389 patients with ES-SCLC. The most common adverse reactions were neutropenia (82.8%), leukopenia (74.0%), anaemia (72.8%), thrombocytopenia (56.0%), alopecia (54.2%), nausea (36.2%), hyperlipidaemia (32.1%), decreased appetite (28.3%), hypoproteinaemia (25.4%), and hyponatraemia (25.4%).
The most common Grade ≥ 3 adverse reactions were neutropenia (65.3%), leukopenia (33.7%), thrombocytopenia (23.1%), anaemia (19.8%), hyponatraemia (10.0%), and lymphopenia (5.1%).
The most common serious adverse reactions were thrombocytopenia (9.3%), neutropenia (7.7%), leukopenia (6.7%), pneumonia (3.3%), and hyperglycaemia or type 1 diabetes mellitus (2.3%).
The most common immune-mediated adverse reactions were hypothyroidism (13.1%), hyperthyroidism (10.8%), immune-mediated adverse skin reactions (7.5%), abnormal liver function (4.1%), immune-mediated lung disease (3.1%), anaemia (2.8%), malaise (2.1%), hyperglycaemia or type 1 diabetes mellitus (1.8%), immune-mediated colitis (1.8%), and platelet count decreased (1.5%).
Serplulimab was discontinued due to adverse reactions in 5.4% of patients.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trial and in post-marketing experience are listed by system organ class and frequency (see Table 2). Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in ASTRUM-005 trial, in which 389 patients were exposed to serplulimab in combination with chemotherapy for a median duration of 22 weeks. See “Pharmacodynamic” for information about the main characteristics of patients in the pivotal clinical trial.
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2. Adverse reactions in patients treated with HETRONIFLY in ASTRUM-005*

Serplulimab with carboplatin and etoposide	
Infections and infestations	
Very common	pneumonia (10.3%) [a]
Common	urinary tract infection [b], respiratory tract infection [c]
Uncommon	septic shock, skin infection, enteritis infectious, lip infection, meningoencephalitis herpetic
Blood and lymphatic system disorders	
Very common	neutropenia (82.8%), leukopenia (74.0%), anaemia (72.8%), thrombocytopenia (56.0%), lymphopenia (20.1%)
Common	coagulation function test abnormal [d], granulocytopenia
Uncommon	lymphadenitis
Immune system disorders	
Common	infusion-related reaction [e]
Uncommon	anaphylactic reaction
Endocrine disorders	
Very common	hypothyroidism (19.5%) [f], hyperthyroidism (12.1%), hyperglycaemia or type 1 diabetes mellitus (15.4%) [g]
Common	thyroid function test abnormal [h], thyroiditis [i]
Uncommon	adrenal insufficiency [j], other thyroid disorder [k], hyperadrenocorticism [l], hypophysitis
Metabolism and nutrition disorders	
Very common	hyperlipidaemia (32.1%), decreased appetite (28.3%), hypoproteinaemia (25.4%), hyperuricaemia (11.8%), electrolyte imbalance (38.3%) [m]
Common	weight decreased, hypoglycaemia
Uncommon	lipoprotein abnormal
Psychiatric disorders	
Very common	Insomnia (12.3%)
Nervous system disorders	
Common	paraesthesia, headache, dizziness, neuropathy peripheral [n]

Uncommon	immune-mediated encephalitis [o], vertigo, neurotoxicity, motor dysfunction
Eye disorders	
Uncommon	vision blurred
Cardiac disorders	
Very common	arrhythmia (10.8%) [p]
Common	sinus tachycardia, conduction defects [q], sinus bradycardia, cardiac failure [r], N-terminal prohormone (*brain natriuretic peptide*) increased, elevated myoglobin in the blood, elevated creatine phosphokinase in the blood, elevated troponin levels
Uncommon	cardiomyopathy [s], myocardial ischaemia, pericardial effusion, myocardial necrosis marker increased, myocarditis
Vascular disorders	
Common	hypertension, vasculitis [t]
Respiratory, thoracic and mediastinal disorders	
Very common	cough (14.9%)
Common	pneumonitis [u], dyspnoea, chest pain
Gastrointestinal disorders	
Very common	nausea (36.2%), constipation (24.7%), abdominal pain (10.5%), diarrhoea (10.3%), vomiting (20.3%)
Common	dysphagia, flatulence, gastrointestinal disorder [v], stomatitis, dyspepsia
Uncommon	dry mouth, enteritis [w], gastritis, immune-mediated pancreatitis, gingival bleeding
Hepatobiliary disorders	
Very common	alanine aminotransferase increased (18.5%), aspartate aminotransferase increased (16.2%), gamma-glutamyltransferase increased (10.0%), alkaline phosphatase increased in the blood (13.1%)
Common	hyperbilirubinaemia, liver injury [x]

Skin and subcutaneous tissue disorders	
Very common	rash (10.0%) [y], alopecia (54.2%)
Common	pruritus, dermatitis [z], hyperhidrosis
Uncommon	pigmentation disorder, psoriasis, dry skin
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain (11.6%) [aa]
Common	arthralgia, pain in extremity, musculoskeletal discomfort [bb]
Uncommon	autoimmune myositis, arthritis
Not known	myositis [cc]
Renal and urinary disorders	
Common	blood urea increased, protein urine present, haematuria, renal injury [dd], blood creatinine increased, glycosuria, white blood cells urine positive
General disorders and administration site conditions	
Very common	pyrexia (16.7 %), asthenia (11.8 %)
Common	fatigue, malaise, oedema [ee]
Uncommon	chills

The following terms represent a group of related events that describe a medical condition rather than a single event:

a. Includes pneumonia, pneumonia fungal.

b. Includes urinary tract infection, asymptomatic bacteriuria.

c. Includes upper respiratory tract infection, pharyngotonsillitis, tonsillitis.

d. Includes activated partial thromboplastin time prolonged, activated partial thromboplastin time, activated partial thromboplastin time shortened, international normalised ratio decreased, prothrombin level increased.

e. Includes drug hypersensitivity, infusion-related reaction.

f. Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, central hypothyroidism, tri-iodothyronine decreased.

g. Includes hyperglycaemia, type 1 diabetes mellitus, diabetic ketoacidosis, blood ketone body increased, glucose tolerance impaired, ketoacidosis.

h. Includes blood thyroid stimulating hormone decreased, tri-iodothyronine increased, anti-thyroid antibody positive, thyroglobulin increased, thyroxine increased.

i. Includes thyroid disorder, thyroiditis.

j. Includes adrenal insufficiency, cortisol decreased.

k. Includes euthyroid sick syndrome, ultrasound thyroid abnormal.

l. Includes cortisol increased, hyperadrenocorticism.

m. Includes hyponatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, hypochloraemia, hyperphosphataemia, hyperkalaemia, hypermagnesaemia, hypercalcaemia.

n. Includes neuropathy peripheral, peripheral sensorimotor neuropathy, immune-mediated neuropathy **.

o. Includes immune-mediated encephalitis, encephalitis autoimmune.

p. Includes supraventricular extrasystoles, supraventricular tachycardia, arrhythmia, ventricular extrasystoles, arrhythmia supraventricular, atrial fibrillation, atrial tachycardia, bradyarrhythmia, early repolarisation syndrome, ventricular arrhythmia, electrocardiogram QT prolonged, electrocardiogram repolarisation abnormality, electrocardiogram T wave abnormal.

q. Includes atrioventricular block first degree, bundle branch block right, atrial conduction time prolongation, bundle branch block left, defect conduction intraventricular.

r. Includes cardiac failure, cardiac failure acute, left ventricular failure.

s. Includes cardiomyopathy, metabolic cardiomyopathy.

t. Includes phlebitis, phlebitis superficial.

u. Includes immune-mediated lung disease, pneumonitis, interstitial lung disease.

v. Includes gastrointestinal haemorrhage, gastrointestinal disorder, lower gastrointestinal haemorrhage.

w. Includes enteritis, immune-mediated enterocolitis **.

x. Includes hepatic function abnormal, drug-induced liver injury, liver injury, immune-mediated hepatitis, immune-mediated hepatic disorder **, hepatic failure **.

y. Includes rash, rash maculo-papular, eczema, drug eruption, erythema, skin toxicity.

z. Includes autoimmune dermatitis, dermatitis, dermatitis allergic, dermatitis bullous, seborrhoeic dermatitis.

aa. Includes back pain, myalgia, musculoskeletal chest pain, spinal pain, neck pain.

bb. Includes muscular weakness, musculoskeletal discomfort.

cc. Includes myositis **, immune-mediated myositis **.

dd. Includes acute kidney injury, renal failure, renal impairment, renal injury.

ee. Includes face oedema, oedema peripheral, peripheral swelling, swelling, swelling face.

** Post-marketing event.

Description of selected adverse reactions

Serplulimab is associated with immune-mediated adverse reactions. The data for the following immune-mediated adverse reactions are based on 1172 patients who received serplulimab monotherapy (n=263) or in combination with other medicinal products (n=909) in eight clinical trials.

Immune-mediated lung disease

Immune-mediated lung disease occurred in 3.5% of patients, including Grade 3, 4 or 5 in 0.9%, 0.1%, and 0.3% of patients, respectively. The median time to onset was 3.25 months (range: 0.03-34.53 months). The median duration was 1.91 months (range: 0.26-13.34 months). 1.6% of patients received high-dose corticosteroid treatment. Immune-mediated lung disease led to discontinuation in 1.0% of patients.

Immune-mediated colitis

Immune-mediated colitis occurred in 2.4% of patients, including Grade 3 in 0.6% of patients and Grade 5 in 0.1% of patients. The median time to onset was 3.01 months (range: 0.03-20.11 months). The median duration was 0.43 months (range: 0.03-4.40 months). 0.5% of patients received high-dose corticosteroid treatment. Immune-mediated colitis led to discontinuation in 0.3% of patients.

Immune-mediated hepatitis

Hepatitis occurred in 0.7% of patients, including Grade 3 in 0.3% of patients, Grade 4 in 0.2% of patients, and Grade 5 in 0.2% of patients. The median time to onset was 2.48 months (range: 0.43-6.60 months). The median duration was 0.95 months (range: 0.53-1.51 months). 0.2% of patients received high-dose corticosteroid treatment. Immune-mediated hepatitis led to discontinuation in 0.3% of patients. Abnormal liver function occurred in 4.5% of patients, including Grade 3 in 1.0% of patients. The median time to onset was 1.51 months (range: 0.07-29.73 months). The median duration was 1.41 months (range: 0.26-17.54 months). 0.3% of patients received high-dose corticosteroid treatment. Abnormal liver function led to discontinuation in 0.3% of patients.

Immune-mediated nephritis and renal insufficiency

Immune-mediated nephritis and renal insufficiency occurred in 2.4% of patients, including Grade 3 in 0.3% of patients and Grade 4 in 0.1% of patients. The median time to onset was 2.78 months (range: 0.23-17.28 months). The median duration was 1.12 months (range: 0.13-5.32 months). 0.2% of patients received high-dose corticosteroid treatment. Immune-mediated nephritis and renal insufficiency led to discontinuation in 0.2% of patients.

Immune-mediated endocrinopathies

Hypothyroidism

Hypothyroidism occurred in 11.2% of patients, including Grade 3 in 0.1% of patients. The median time to onset was 3.84 months (range: 0.62-34.10 months). The median duration was 2.76 months (range:

0.53-7.49 months). 5.9% of patients received thyroid hormone replacement therapy. No patients discontinued serplulimab due to hypothyroidism.

Hyperthyroidism

Hyperthyroidism occurred in 6.3% of patients, and there were no cases of Grade ≥ 3 hyperthyroidism. The median time to onset was 1.79 months (range: 0.69-31.18 months). The median duration was 1.41 months (range: 0.07-4.21 months). No patients discontinued serplulimab due to hyperthyroidism.

Thyroiditis

Thyroiditis occurred in 0.7% of patients, and there were no cases of Grade ≥ 3 thyroiditis. The median time to onset was 5.65 months (range: 1.94-13.50 months). The median duration was 5.93 months (range: 0.56-11.30 months). 0.2% of patients received thyroid hormone replacement therapy. No patients discontinued serplulimab due to thyroiditis.

Adrenal gland disorders

Adrenal gland disorders occurred in 0.3% of patients, all of which were Grade 2. The median time to onset was 5.78 months (range: 5.75-6.93 months). No patients discontinued serplulimab due to adrenal gland disorders.

Pituitary disorders

Pituitary disorders occurred in 0.9% of patients, including Grade 3 in 0.2% of these cases. The median time to onset was 6.97 months (range: 1.41-20.53 months). The median duration was 2.43 months. 0.3% of patients received high-dose corticosteroid treatment. Pituitary disorders led to discontinuation in 0.2% of patients.

Type 1 diabetes mellitus/hyperglycaemia

Type 1 diabetes mellitus/hyperglycaemia occurred in 1.0% of patients, including Grade 3 in 0.5% of patients and Grade 4 in 0.1% of patients. The median time to onset was 4.09 months (range: 0.69-11.10 months). The median duration was 2.96 months. 0.6% of patients received insulin replacement therapy. Type 1 diabetes mellitus/hyperglycaemia led to discontinuation in 0.1% of patients.

Immune-mediated adverse skin reactions

Immune-mediated adverse skin reactions occurred in 8.7% of patients, including Grade 3 in 0.8% of patients. The median time to onset was 2.10 months (range: 0.03-30.52 months). The median

duration was 0.82 months (range: 0.07-12.39 months). 1.4% of patients received high-dose corticosteroid treatment. Immune-mediated adverse skin reactions led to discontinuation in 0.4% of patients.

Immune-mediated pancreatitis

Immune-mediated pancreatitis occurred in 1.1% of patients, including Grade 3 in 0.3% of patients, Grade 4 in 0.2% of patients and Grade 5 in 0.1% of patients. The median time to onset was 2.30 months (range: 0.23-12.42 months). The median duration was 0.76 months (range: 0.16-10.12 months). 0.2% of patients received high-dose corticosteroid treatment. Immune-mediated pancreatitis led to discontinuation in 0.2% of patients.

Immune-mediated myocarditis

Immune-mediated myocarditis occurred in 0.6% of patients, including Grade 3 in 0.2% of patients and Grade 5 in 0.1% of patients. The median time to onset was 1.87 months (range: 0.26-25.36 months). The median duration was 0.89 months (range: 0.72-4.57 months). 0.3% of patients received high-dose corticosteroid treatment. Immune-mediated myocarditis led to discontinuation in 0.2% of patients.

Immune-mediated uveitis

Immune-mediated uveitis occurred in 0.1% of patients, which was Grade 1. The time to onset was 6.90 months. The duration of immune-mediated uveitis was 1.35 months. The event resolved in the patient.

Other immune-mediated adverse reactions

Other clinically significant immune-mediated adverse reactions reported in patients who received serplulimab were as follows. Severe or fatal cases have been reported for some of these adverse reactions.

Blood and lymphatic system disorders

Anaemia, leukopenia, thrombocytopenia, neutropenia.

Nervous system disorders

Dizziness, immune-mediated encephalitis, neuropathy peripheral.

Eye disorders

Vision blurred.

Cardiac/vascular disorders

Acute coronary syndrome, myocardial infarction, cardiac failure acute, cardiotoxicity, troponin increased.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, chronic obstructive pulmonary disease, respiratory failure.

Gastrointestinal disorders

Mouth ulceration, vomiting, proctitis.

General disorders and administration site conditions

Aasthenia, fatigue, pyrexia.

Other

Panic disorder, tinnitus, cholangitis acute, sepsis, cortisol decreased, blood alkaline phosphatase increased, electrolyte imbalance.

Infusion-related reactions

Infusion-related reactions occurred in 1.4% of patients, including Grade 3 in 0.2% of patients and Grade 4 in 0.1% of patients. The median time to onset was 1.02 months (range: 0.03-9.86 months). The median duration was 0.07 months (range: 0.03-0.53 months). No patients discontinued serplulimab due to infusion-related reactions.

Laboratory abnormalities

The proportions of patients who experienced a shift from baseline to a Grade ≥ 3 laboratory abnormality were as follows: 0.6% for platelet count decreased, 0.4% for neutrophil count decreased, 0.3% for blood creatine phosphokinase increased, 0.2% for white blood cell count decreased, 0.1% for blood lactate dehydrogenase increased, and 0.1% for blood cholesterol increased.

Elderly patients

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients. Data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

Reporting suspected adverse reactions

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

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

Properties/Effects

ATC code

L01FF12

Mechanism of action

Serplulimab (HLX10) is a humanised monoclonal IgG4 antibody, which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Clinical efficacy

The efficacy of serplulimab in combination with chemotherapy (carboplatin plus etoposide) for the first-line treatment of ES-SCLC was evaluated in ASTRUM-005 trial (NCT04063163), a phase 3, randomised, double-blind, multiregional clinical trial. The primary efficacy endpoint was overall

survival (OS). Secondary efficacy endpoints were progression free survival (PFS), objective response rate (ORR) and duration of response (DOR) as assessed by independent radiology review committee (IRRC) and investigator based on RECIST 1.1.

The trial included adult patients (18 years or older) with ES-SCLC (according to the Veterans Administration Lung Study Group [VALG] staging system) who had not been treated with systemic therapy and with an ECOG performance-status score of 0 or 1. Patients were excluded if they had active or untreated central nervous system metastases; active autoimmune disease; administration of systemic immunosuppressive medicinal products within 14 days prior to the first dose.

A total of 585 patients were enrolled and randomised (2:1) to receive one of the treatment regimens Arm A: serplulimab (4.5 mg/kg) + carboplatin (AUC=5, up to 750 mg) + etoposide (100 mg/m^2) administered via intravenous infusion every 3 weeks for 4 cycles of induction therapy, followed by maintenance therapy with serplulimab (4.5 mg/kg) every 3 weeks; Arm B: Placebo + carboplatin (AUC=5, up to 750 mg) + etoposide (100 mg/m^2) administered via intravenous infusion every 3 weeks for 4 cycles of induction therapy, followed by maintenance therapy with placebo (4.5 mg/kg) every 3 weeks. Etoposide was administered on days 1, 2 and 3 of each cycle. Carboplatin and etoposide were administered until completion of 4 cycles, the occurrence of progressive disease or unacceptable toxicity, whichever occurred first. Serplulimab was administered until disease progression or unacceptable toxicity.

Randomisation was stratified by PD-L1 expression level (negative: tumour proportion scores [TPS] < 1%, positive: TPS ≥ 1%, or not evaluable/not available, measured by PD-L1 IHC 22C3 pharmDx kit), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years).

Baseline characteristics were balanced between the treatment arms. Among the patients enrolled, 68.5% were Asian (401 patients), and 31.5% were non-Asian (184 patients), all of which were White. The median age was 62 years (range: 28-83) with 39.3% of patients ≥ 65 years of age, and 1.9% of patients ≥ 75 years of age. 82.2% of patients were men. Baseline ECOG performance-status score was 0 (17.6%) or 1 (82.4%). 16.9% of patients were PD-L1 positive (TPS ≥ 1%). 13.3% of patients had a history of brain metastases.

At the time of the interim analysis cut-off on 22 October 2021 (25 months after the start of the study) when 66% of predefined OS events were observed (defined approximately 226, actual 246 OS events), patients had a median survival follow-up time of 12.3 months. OS, PFS and ORR results from the interim analysis are summarised in Table 3.

Table 3. Efficacy data at the primary analysis (data cut-off date: 22 October 2021)

	Arm A (Serplulimab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)

Number of patients		389	196
Primary endpoint			
OS	Number of patients with events, n (%)	146 (37.5 %)	100 (51.0 %)
	Median OS (months)	15.4	10.9
	Hazard ratio (95% CI)	0.63 (0.49-0.82)	
	p-value	< 0.001	
Secondary endpoints			
PFS -IRRC per RECIST 1.1	Median PFS (months)	5.7	4.3
	Hazard ratio (95% CI)	0.48 (0.38-0.59)	

Updated analysis after unblinding (after primary analysis) with longer follow-up duration (median: 19.7 months) was conducted by the cut-off date 13 June 2022 when 100% of predefined OS events were observed (defined approximately 342, actual 363 OS events). The median OS was 15.8 months in the serplulimab group and 11.1 months in the placebo group. The stratified HR (95% CI) was 0.62 (0.50, 0.76).

Immunogenicity

The immunogenicity of serplulimab was evaluated in 389 patients treated with serplulimab at 4.5 mg/kg Q3W in the ASTRUM-005 trial. Seven patients (1.8%) were ADA positive at any visit, of whom 6 patients (1.5%) were treatment-emergent ADA positive, defined as at least one post-baseline ADA positive.

In dose escalation and dose expansion study HLX10-001, ADAs were observed in 13 out of 66 patients (19.7%).

Neutralising antibodies were not observed in either of the key studies. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However, data are still limited.

Pharmacokinetics

Serplulimab pharmacokinetics has been investigated in a population pharmacokinetic (popPK) analysis that included 1144 patients with lung cancer (including ES-SCLC) and other solid cancer types from 8 studies. The patients received serplulimab intravenously as monotherapy or combination therapy in the dose range of 0.3 to 10 mg/kg Q2W, 4.5 mg/kg Q3W, 200 mg Q2W, 300 mg Q3W and 400 mg Q4W. The PK was described by a two-compartment model with time-dependent clearance (CL). Inter-individual variability (coefficient of variation, CV) in base CL and central volume of distribution (Vc) was 25.8% and 15.4%. The mean (CV) observed trough concentration at steady state in the ASTRUM-005 trial was 62.5 µg/ml (36.3%).

Absorption

Serplulimab is administered by intravenous infusion and is therefore immediately and completely bioavailable. Other routes of administration have not been investigated.

Distribution

Based on a popPK analysis the volume of distribution of serplulimab is approximately 5.73 l.

Metabolism

The metabolic pathway of serplulimab has not been characterised. Serplulimab is expected to be catabolised into small peptides and amino acids by general protein degradation processes.

Elimination

Based on a popPK analysis, serplulimab clearance (CL) after the first dose is 0.225 l/day. The clearance decreases over time by a maximum of 30.5% (CV 26.3%) with 106 days to reach half of the maximum effect. The half-life at steady state is approximately 24.3 days.

Linearity/non-linearity

Serplulimab exhibited linear pharmacokinetics over the dose range of 0.3 to 10 mg/kg Q2W (including flat doses of 200 mg Q2W, 300 mg Q3W and 400 mg Q4W) both after single and multiple doses.

Kinetics in specific patient groups

No dedicated studies have been performed in special populations. A popPK analysis suggested no difference in the total systemic clearance of serplulimab based on age (23-83 years), race (n=247

Whites and n=895 Asians), and ECOG performance-status score (0 or 1). Serplulimab clearance increased with increasing body weight.

Hepatic impairment

No effect of ALT, AST or total bilirubin was found on serplulimab CL based on a popPK analysis in patients with mild (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST; n=176) and moderate (bilirubin > 1.5 to 3 × ULN and any AST; n=2) hepatic impairment, and normal (bilirubin ≤ ULN and AST ≤ ULN; n=956) hepatic function. There are insufficient data in patients with moderate hepatic impairment for dosing recommendations. Serplulimab has not been studied in patients with severe (bilirubin > 3 × ULN and any AST) hepatic impairment (see “Dosage/Administration”).

Renal impairment

No effect of creatinine or creatinine clearance (CRCL) (Cockcroft-Gault) was found on serplulimab CL based on a popPK analysis in patients with mild (CRCL=60-89 ml/min; n=448), moderate (CRCL=30-59 ml/min; n=102), and severe (CRCL=15-29 ml/min; n=1) renal impairment, and normal renal function (CRCL≥ 90 ml/min, n=591). There are insufficient data in patients with severe renal impairment for dosing recommendations (see “Dosage/Administration”).

Preclinical data

Repeat-dose toxicity

In the repeat-dose toxicity study in cynomolgus monkeys dosed for up to 31 weeks, a high incidence of pharmacology-related perivascular mononuclear cell infiltration in the brain choroid plexus was observed at 100 mg/kg. The no observed adverse effect level (NOAEL) in the 31-weeks toxicity study was 50 mg/kg/week, which produced exposure 36 times (calculated by AUC_{0-t}) the exposure in humans at dose of 3 mg/kg every two weeks.

Reproductive toxicity

Reproductive toxicity studies have not been performed.
The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.
Two anti-PD-L1 monoclonal antibodies were evaluated in cynomolgus monkeys for reproductive and developmental toxicity and were shown to cause premature delivery, foetal loss and premature neonatal death when administrated to pregnant monkeys.

Therefore, potential risks of administering serplulimab during pregnancy include increased rates of abortion or stillbirth. Based on its mechanism of action, foetal exposure to serplulimab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders that have been reported in PD-1 knockout mice.

Genotoxicity and carcinogenicity

No studies have been performed to assess the genotoxic or carcinogenic potential of serplulimab.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in “Instructions for handling” HETRONIFLY should not be infused concomitantly in the same intravenous line with other medicinal products.

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.

Shelf life after opening

Diluted solution

From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C. This 24-hour hold may include up to 6 hours at room temperature (≤ 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

Special precautions for storage

Store in the refrigerator (2–8 °C), in the original packaging, protected from light and out of the reach of children.
Do not freeze. Do not shake.

Instructions for handling

Preparation and administration

- Aseptic handling should be ensured during the preparation of infusion.

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25°C).
- The product should be inspected visually for the particulate matters and discoloration prior to administration. The concentrate is a colourless to slightly yellow, clear to slightly opalescent solution. Discard the vial if visible particles are observed.
- Confirm the dose of the product and calculate the required volume of HETRONIFLY.
- Withdraw a volume of sodium chloride 9 mg/ml (0.9%) solution for injection corresponding to the volume of infused product from the target intravenous bag using a sterile syringe and discard.
- Use a syringe to withdraw the required volume of HETRONIFLY from the vial and inject it into the sodium chloride 9 mg/ml (0.9%) solution for injection to prepare a diluted solution with a final concentration range from 1.0 to 8.0 mg/ml. Mix the diluted solution by gentle inversion.
- Administer the infusion solution intravenously using a sterile, non-pyrogenic, low-protein binding 0.2 to 5.0 µm in-line or add-on filter.
- Set the initial infusion rate to 100 ml per hour (25 drops per minute is recommended). The infusion rate can be adjusted if infusion-related reactions occur (see “Dosage/Administration”). If there is no infusion-related adverse reaction in the first infusion, the duration of subsequent administration can be shortened to 30 minutes (± 10 minutes).
- From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, the diluted solution can be stored for 24 hours at 2°C to 8°C. This 24- hour hold may include up to 6 hours at room temperature (≤ 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use (see “Shelf life after opening”).
- At the end of infusion, the infusion tube is flushed with sodium chloride 9 mg/ml (0.9%) solution according to the routine operation procedure of the hospital.
- Do not co-administer other medical products through the same infusion line.
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded in the patient file.

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

Authorisation number

69906 (Swissmedic)

Packs

HETRONIFLY 100 mg/10 ml: 1 vial [A]

Marketing authorisation holder

Accord Healthcare AG, 4103 Bottmingen.

Date of revision of the text

May 2025