ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

HETRONIFLY 10 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 10 mg of serplulimab.
One vial of 10 ml of concentrate contains 100 mg of serplulimab.

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.

Excipient with known effect
Each 10 ml vial contains 0.98 mmol (22.5 mg) sodium and 2.0 mg polysorbate 80 (E 433).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colourless to slightly yellow, clear to slightly opalescent solution, pH 5.2-5.8, osmolality of approximately 280-340 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.

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 section 4.4)
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 section 4.4).

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
	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 occurred for the first time Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Withhold until adverse reactions recover or improve to Grade 1
	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 occurred for the first time	Permanently discontinue

Adverse reactions	Severity	Treatment modification[#]
	Grade 4 or recurrent Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	
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 replacement hormones (see sections 4.4 and 4.8).
[†]: 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 populations

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 5.1 and section 5.2).

Renal impairment
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 section 5.2).

Hepatic impairment
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 impairments and no data are available in severe (bilirubin > 3 × ULN and any AST) hepatic impairments. No dose recommendation can be made for patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population
There is no relevant use of serplulimab in the paediatric population in the indication of small cell lung cancer.

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 section 6.6).

For instructions on dilution and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving serplulimab (see section 4.8). Most immune-mediated adverse reactions occurring during treatment were reversible and managed by withholding treatment, administration of corticosteroids, and/or supportive care (see section 4.2). 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 aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, treatment should be withheld, and corticosteroid administered. For most Grade 2 and some specific Grade 3 or 4 immune-mediated adverse reactions, administration should be withheld until recover or improve 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), corticosteroid (1-2 mg/kg/day prednisone or equivalent) and other symptomatic treatments should be given according to the clinical symptoms until recover or improve 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 lung disease

Immune-mediated pneumonitis, including fatal cases, has been reported in patients receiving HETRONIFLY (see section 4.8). 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, and other causes excluded. For treatment modification, see section 4.2.

Immune-mediated colitis

Immune-mediated colitis, including fatal cases, has been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2. 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 section 4.8). Patients should be monitored for changes in liver function and clinical signs and symptoms of immune-mediated hepatitis such as transaminase and total bilirubin elevations periodically (every month). 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 section 4.2.

Immune-mediated nephritis and renal insufficiency

Immune-mediated nephritis and renal insufficiency has been reported in patients receiving serplulimab (see section 4.8). Patients should be monitored for changes in renal function and clinical signs and symptoms of immune-mediated nephritis and renal insufficiency periodically (every month). The frequency of renal function test 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 section 4.2.

Immune-mediated endocrinopathies

Thyroid diseases
Thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis, have been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

Pituitary disorders
Hypophysitis has been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

Adrenal insufficiency
Adrenal insufficiency has been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

Hyperglycaemia
Hyperglycaemia or type 1 diabetes mellitus has been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

Immune-mediated skin reactions

Immune-mediated skin reactions have been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

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 section 4.8). 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 section 4.2).

Immune-mediated myocarditis

Immune-mediated myocarditis, including fatal cases, has been reported in patients receiving serplulimab (see section 4.8). 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 section 4.2).

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 section 4.8). 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 section 4.2).

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 section 4.2).

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.

Excipients with known effect

This medicinal product contains 0.98 mmol (or 22.5 mg) sodium per 10 ml vial, equivalent to 1.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 2.0 mg of polysorbate 80 (E 433) in each 10 ml vial. Polysorbates may cause allergic reactions.

For instructions on dilution and handling of the medicinal product before administration, see section 6.6.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 HETRONIFLY.

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 section 4.4).

4.6 Fertility, pregnancy and 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 section 5.3). 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, which is decreasing to low concentrations soon; consequently, a risk to the breast-fed infant cannot be excluded during this short 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.

4.7 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 section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that serplulimab does not adversely affect them.

4.8 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 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 section 5.1 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 (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); 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 [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, leukopenia, anaemia, thrombocytopenia, lymphopenia
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 [f], hyperthyroidism, hyperglycaemia or type 1 diabetes mellitus [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, decreased appetite, hypoproteinaemia, hyperuricaemia, electrolyte imbalance [m]
Common	weight decreased, hypoglycaemia
Uncommon	lipoprotein abnormal
Psychiatric disorders	
Very common	insomnia
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 [p]
Common	sinus tachycardia, conduction defects [q], sinus bradycardia, cardiac failure [r], N-terminal prohormone brain natriuretic peptide increased
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
Common	pneumonitis [u], dyspnoea, chest pain
Gastrointestinal disorders	
Very common	nausea, constipation, abdominal pain, diarrhoea, vomiting
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, aspartate aminotransferase increased, gamma-glutamyltransferase increased
Common	hyperbilirubinaemia, liver injury [x]
Skin and subcutaneous tissue disorders	
Very common	rash [y], alopecia
Common	pruritus, dermatitis [z], hyperhidrosis
Uncommon	pigmentation disorder, psoriasis, dry skin
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain [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, asthenia
Common	fatigue, malaise, oedema [ee]
Uncommon	chills
Investigations	
Very common	blood alkaline phosphatase increased
Common	myoglobin blood increased, blood creatine phosphokinase increased, troponin increased

[*] Adverse reaction frequencies presented in Table 2 may not be fully attributable to HETRONIFLY alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

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 1 172 patients who received serplulimab monotherapy (n=263) or in combination with other medicinal products (n=909) across eight doses (0.3, 1, 3, 10 mg/kg every 2 weeks, 4.5 mg/kg every 3 weeks, 200 mg every 2 weeks, 300 mg every 3 weeks, or 400 mg every 4 weeks) in eight clinical trials. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

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. 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 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 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 patients. 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 skin reactions

Immune-mediated 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: 0.03-30.52months). The median duration was 0.82 months (range: 0.07-12.39 months). 1.4% of patients received high-dose corticosteroid treatment. Immune-mediated 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 for 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: anaemia, leukopenia, thrombocytopenia, neutropenia.

Nervous system: dizziness, immune-mediated encephalitis, neuropathy peripheral.

Eye disorders: vision blurred.

Cardiac/vascular: acute coronary syndrome, myocardial infarction, cardiac failure acute, cardiotoxicity, troponin increased.

Respiratory, thoracic and mediastinal: dyspnoea, chronic obstructive pulmonary disease, respiratory failure.

Gastrointestinal: mouth ulceration, vomiting, proctitis.

General disorders and administration site conditions: asthenia, 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

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 of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PD-L1 (Programmed cell death-1/death ligand 1) inhibitors
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.

The PD-1 receptor occupation of peripheral T cells and interleukin-2 (IL-2) release ability in vitro were studied in the phase 1 trial involving 29 Chinese patients with advanced solid tumour that were injected with single and multiple doses (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg) of serplulimab. The result showed that serplulimab could stably maintain the saturation state of receptor occupation and sustained functional blockage at the dosage from 0.3 mg/kg to 10 mg/kg every 2 weeks interval.

Clinical efficacy and safety

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. Analysis for the primary endpoint was performed at 25 and 33 months since the start of the clinical trial. The study treatment regimens were unblinded after the primary analysis.

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 described in Table 3. 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).

Table 3. Intravenous treatment regimens

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Serplulimab (4.5 mg/kg) [a] + carboplatin (AUC=5, up to 750 mg) [b] + etoposide (100 mg/m^2) [b,c]	Serplulimab (4.5 mg/kg) [a]
B	Placebo + carboplatin (AUC=5, up to 750 mg) [b] + etoposide (100 mg/m^2) [b,c]	Placebo

a. Serplulimab was administered until disease progression or unacceptable toxicity.
b. Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurred first.
c. Etoposide was administered on day 1, 2 and 3 of each cycle.

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 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 4.

Table 4. 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)	
Confirmed ORR	(%)	67.4%	58.7%
Median DOR	Months (95% CI)	5.8 (5.2-7.5)	4.1 (3.0-4.2)

Updated analysis after unblinding 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). The median PFS by IRRC assessment per RECIST 1.1 was 5.7 months and 4.3 months, respectively, with a stratified HR (95% CI) of 0.47 (0.38, 0.58). The efficacy results of final analysis were consistent with the primary analysis. Kaplan-Meier curves for OS and PFS of final analysis are presented in Figures 1 and 2.

Figure 1. Kaplan-Meier curve of OS in overall population at the updated analysis (ITT) (data cut-off date: 13 June 2022)

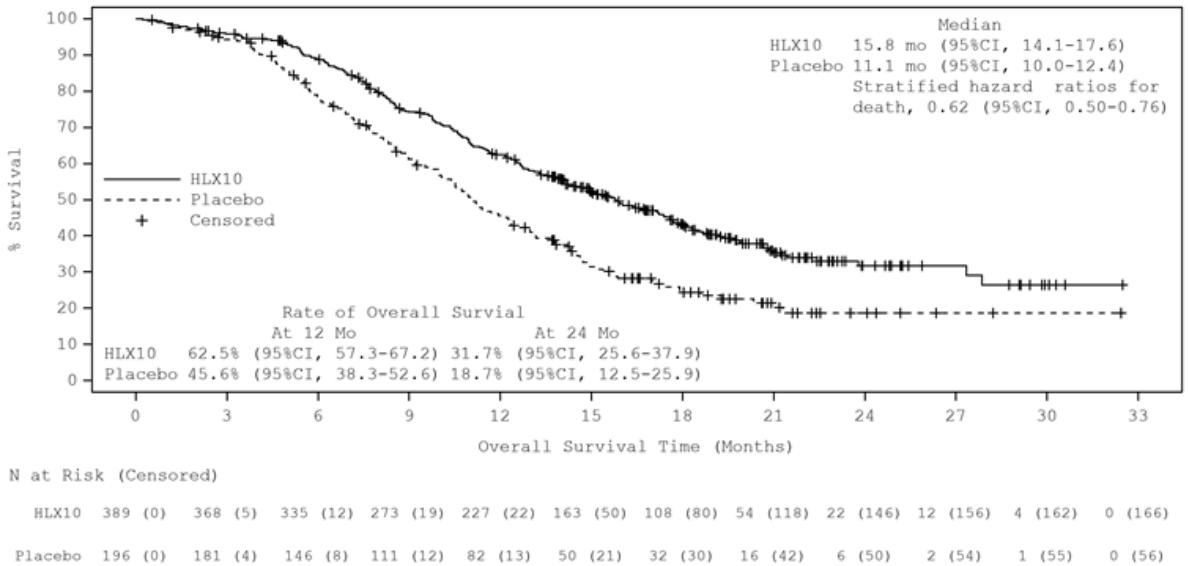
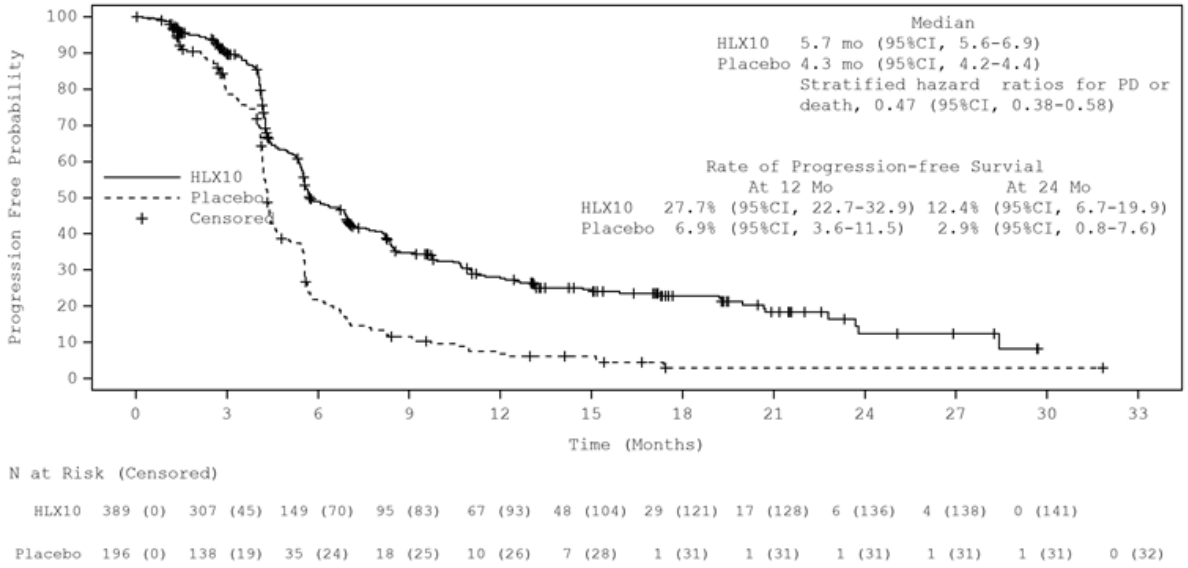


Figure 2. Kaplan-Meier curve of PFS (RECIST 1.1) by IRRC in overall population at the updated analysis (ITT) (data cut-off date: 13 June 2022)



N at Risk (Censored)

HLX10	389 (0)	307 (45)	149 (70)	95 (83)	67 (93)	48 (104)	29 (121)	17 (128)	6 (136)	4 (138)	0 (141)	
Placebo	196 (0)	138 (19)	35 (24)	18 (25)	10 (26)	7 (28)	1 (31)	1 (31)	1 (31)	1 (31)	1 (31)	0 (32)

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.

Elderly patients

In the ASTRUM-005 trial, of the 389 patients in the serplulimab group in the overall population, 153 (39.3%) were ≥ 65 years. No overall differences in efficacy were observed between elderly patients and younger patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with serplulimab in all subsets of the paediatric population for lung cancer (small cell and non-small cell lung cancer) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Serplulimab pharmacokinetics has been investigated in a population pharmacokinetic (popPK) analysis that included 1 144 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.

Biotransformation

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.

Special populations

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.

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 section 4.2).

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 section 4.2).

5.3 Preclinical safety 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 $AUC_{0\text{-}t}$) 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (for pH-adjustment)
Sodium citrate (E331) (for pH-adjustment)
Sodium chloride
Mannitol (E421)
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6. HETRONIFLY should not be infused concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

Unopened vial

3 years.

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of concentrate in a 10 ml Type I clear glass vial with chlorobutyl rubber stopper and aluminium-plastic combination caps containing 100 mg of serplulimab.

Pack of 1 vial.

6.6 Special precautions for disposal and other 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 section 4.2). 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 section 6.3).
- 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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n

Edifici Est, 6a Planta
08039 Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1870/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2025

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

Shanghai Henlius Biopharmaceutical Co., Ltd.
(Building D) Block 1
No. 1289 Yishan Road
Xuhui District, Shanghai
China

Name and address of the manufacturer responsible for batch release

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50, Pabianice, 95-200, Poland

Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,
Schimatari, 32009, Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

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

The marketing authorization holder (MAH) shall submit the first PSUR for this product within 6 months following authorization.

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

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

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

• Additional risk minimisation measures

The MAH shall ensure that in each Member State where HETRONIFLY is marketed, all patients/caregivers who use HETRONIFLY are provided with the patient educational material.

• **Composition of educational material package:**

- Summary of product characteristics/package leaflet (will be voluntarily provided)
- Patient card

• **Risks covered by the educational material:**

- Immune-mediated adverse reactions
- Severe infusion reactions

The Education Material includes information on the signs and symptoms of immune-mediated adverse reactions and infusion-related reactions, as well as the guidance for the importance of patient monitoring and the clinical management of these events. The material will be distributed to relevant HCPs as a package and patients will receive their materials through the HCP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HETRONIFLY 10 mg/ml concentrate for solution for infusion
serplulimab

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 10 mg of serplulimab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate, sodium chloride, mannitol, polysorbate 80, water for injections.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
100 mg/10 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution.
Read the package leaflet before use.
Do not shake.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n
Edifici Est, 6ª Planta
08039 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1870/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

HETRONIFLY 10 mg/ml sterile concentrate
serplulimab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/10 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

HETRONIFLY 10 mg/ml concentrate for solution for infusion
serplulimab

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

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

What is in this leaflet

1. What Hetronifly is and what it is used for

Hetronifly is a cancer medicine that contains the active substance serplulimab. It is a monoclonal antibody, a type of protein that is designed to recognise and attach to a specific target in the body called programmed death-1 (PD-1) receptor which is found on the surface of T and B cells (types of white blood cells that form part of the immune system, the body's natural defences). When PD-1 is activated by cancer cells it can switch off the activity of T cells. By blocking PD-1, Hetronifly prevents it from switching off your T cells which helps your immune system fight the cancer.

Hetronifly is used to treat adults with a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC). It is used when the cancer:
- has spread within the lungs (or to other parts of the body) and
- has not previously been treated.

If you have any questions about how Hetronifly works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

Hetronifly will be given in combination with chemotherapy. It is important that you also read the package leaflets for the specific chemotherapy you may be receiving. Ask your doctor If you have any questions about these medicines.

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

You should not be given Hetronifly
If you are allergic to serplulimab or any of the other ingredients of this medicine.
If you are not sure if you are allergic, talk to your doctor or nurse before you are given Hetronifly.

Warnings and precautions
Talk to your doctor before you are given Hetronifly if you have:
- an autoimmune disease (an illness where´s immune system attacks its own cells)
- liver problems
- kidney damage
- lung problems or breathing problems
- had an organ transplant
- had an allergic reaction to other cancer medicines that work the same way (monoclonal antibody therapies)

If any of the above applies to you (or you are not sure), talk to your doctor before you are given Hetronifly.

When you are given Hetronifly you can have some serious side effects (See section 4).

If you have any of the following conditions, call or see your doctor straight away. Your doctor may give you other medicines that prevent more severe complications and to help reduce your symptoms. Your doctor may delay the next dose of Hetronifly or stop your treatment with Hetronifly.

Speak with your doctor immediately if you notice any of the following symptoms:
- inflammation of the lungs: symptoms may include new or worsening cough, shortness of breath or chest pain
- inflammation of the liver and bile ducts: symptoms may include nausea or vomiting, feeling less hungry, pain on the right side of your stomach, yellowing of skin or whites of eyes, drowsiness, dark urine or bleeding or bruising more easily than normal
- inflammation of the intestines: symptoms may include diarrhoea or more bowel movements than usual, or stools that are black, tarry or sticky with blood or mucus, severe stomach pain or tenderness
- inflammation of the kidneys: symptoms may include a decrease in the amount of urine you pass
- inflammation of the skin: symptoms may include rash, itching, skin blistering or ulcers in the mouth or on other moist surfaces
- inflammation of glands (especially the thyroid, adrenal, pituitary and pancreas): symptoms may include fast heart rate, extreme tiredness, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches, abdominal pain, nausea and vomiting
- type 1 diabetes: symptoms may include high blood sugar, feeling more hungry or thirsty than usual, passing urine more often than usual, fast and deep breathing, confusion, or a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat
- infusion-related reactions: symptoms may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever
- inflammation of the heart muscle: symptoms may include chest pain, shortness of breath, or irregular heartbeat
- inflammation or problems of the muscles: symptoms may include muscle pain, or muscle weakness or rapid fatigue
- inflammation of the brain (encephalitis): symptoms may include seizures, headache, fever, chills, vomiting, confusion and memory problems
- inflammation of the eyes, which may include changes in eyesight
- low number of platelets: symptoms may include bleeding (nose or gum bleeding) and/or bruising

Children and adolescents
Hetronifly is not recommended for anyone under the age of 18 years. This is because there is no information on how well it works in this age group.

Other medicines and Hetronifly
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Tell your doctor if you are taking other medicines that weaken your immune system, examples include cortisone derivatives, such as prednisone. These medicines may interfere with the way Hetronifly works. However, once you are treated with Hetronifly, your doctor may give you cortisone derivatives to reduce possible side-effects with Hetronifly. Cortisone derivatives may also be given to you before receiving Hetronifly in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by chemotherapy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must not use Hetronifly if you are pregnant unless your doctor specifically recommends it. Hetronifly can harm your unborn baby.

Breast-feeding
It is not known if serplulimab passes into breast milk. You and your doctor will decide if you should breast-feed after receiving serplulimab.

Driving and using machines
Hetronifly may cause fatigue and other adverse reactions. Do not drive or use machines after you have been given Hetronifly unless you are sure you are feeling well.

Hetronifly contains sodium
This medicine contains 22.5 mg of sodium (main component of cooking/table salt) in each 10 ml vial. This is equivalent to 1.1 % of the recommended maximum daily dietary intake of sodium for an adult.

Hetronifly contains polysorbate 80
This medicine contains 2.0 mg of polysorbate 80 in each 10 ml vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How you are given Hetronifly

Hetronifly will be given to you in a hospital or clinic under the supervision of an experienced doctor.

The recommended dose is 4.5 mg per kg of your body weight every 3 weeks.

Your doctor will give you Hetronifly via an infusion (drip) into your vein. The first infusion is given over a period of about 1 hour. The next infusions are given over a period of 30 minutes.

If you take more Hetronifly than you should
There is no information on overdose with serplulimab. This medicine is given to you by an experienced professional. Chance of an overdose is low. In case of overdose, you will be closely monitored for signs or symptoms of adverse reactions. Your doctor will start appropriate treatment.

If you miss an appointment to get Hetronifly
It is very important that you do not miss a dose of this medicine. If you miss an appointment, call your doctor straight away to reschedule your appointment.

If you stop receiving Hetronifly
Stopping treatment may stop the effect of the medicine. Do not stop treatment with Hetronifly unless you have discussed this with your doctor.

If you have any further questions about your treatment, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Be aware of important symptoms of inflammation.
Hetronifly acts on your immune system and may cause inflammation in parts of your body. This may seriously damage your body. Some inflammatory conditions may be life-threatening and need treatment or withdrawal of Hetronifly (see section 2).

Serious side effects
Speak with your doctor immediately if you notice any of the following serious symptoms. They may be signs of a serious, possibly fatal, condition. Getting medical treatment right away may help keep these problems from becoming more serious.

- inflammation of the lungs (*common*): symptoms may include new or worsening cough, shortness of breath or chest pain
- inflammation of the liver and bile ducts (*common*): symptoms may include nausea or vomiting, feeling less hungry, pain on the right side of your stomach, yellowing of skin or whites of eyes, drowsiness, dark urine or bleeding or bruising more easily than normal
- inflammation of the intestines (*uncommon*): symptoms may include diarrhoea or more bowel movements than usual, or stools that are black, tarry or sticky with blood or mucus, severe stomach pain or tenderness
- inflammation of pancreas (*uncommon*): symptoms may include abdominal pain, nausea and vomiting
- inflammation of the heart muscle (*uncommon*): symptoms may include chest pain, shortness of breath, or irregular heartbeat

Other side effects
Talk to your doctor if you get any of the following side effects that have been reported in clinical trials with patients receiving Hetronifly in combination with chemotherapy:

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

- infection of the lung (pneumonia)
- decrease in the number of white blood cells (leukocytes, neutrophils, lymphocytes), red blood cells (anaemia) or platelets (thrombocytopenia)
- reduced thyroid gland activity (can cause tiredness or weight gain) or overactive thyroid gland activity
- blood tests showing high levels of glucose (hyperglycaemia or type 1 diabetes mellitus)
- blood tests showing high levels of uric acid (hyperuricaemia) or lipids (hyperlipidaemia)
- blood tests showing abnormal levels of electrolyte (potassium, sodium, calcium, magnesium, phosphate, or chloride)
- blood tests showing low levels of protein (hypoproteinaemia)
- reduced appetite
- trouble sleeping
- abnormal heart rhythm
- cough
- nausea
- constipation
- abdominal pain
- diarrhoea
- vomiting
- increased liver enzyme levels in the blood (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase)
- rash

- hair loss
- pain in the muscles and bones
- fever
- weakness
- increased levels of alkaline phosphatase in the blood

Common (may affect up to 1 in 10 people)
- infection of urinary tract
- infection of upper respiratory tract
- abnormal coagulation function test
- infusion-related reaction
- inflammation of thyroid gland, abnormal thyroid function test
- weight loss
- low blood sugar level
- damage to the peripheral nervous system causing numbness, dizziness, headache, disorder of sensation (paraesthesia)
- a regular cardiac rhythm in which heart beats faster than normal, slow heartbeat, conduction defects, heart failure, increased level of substances in the brain (natriuretic peptide) which may be a sign of heart failure
- high blood pressure, inflammation of the blood vessels
- inflammation of the mouth mucosa, indigestion, difficulty swallowing, abdominal distension, gastrointestinal disorder
- increased blood bilirubin (breakdown product of haemoglobin)
- itchiness, inflammation of the skin, excessive sweating
- joint pain (arthralgia), pain in arms or legs, musculoskeletal discomfort
- glucose in the urine, protein urine present, positive red or white blood cells in the urine, renal injury
- increased level of urea or creatinine in the blood
- feeling tired, overall discomfort, swelling
- increased level of myocardial necrosis marker (troponin), myoglobin or creatine phosphokinase in the blood

Uncommon (may affect up to 1 in 100 people)
- severe infection, skin infection, infection of intestine, lip infection, infection of the brain and brain covering caused by herpes simplex virus
- inflammation of the lymph node
- anaphylactic reaction
- decreased secretion of hormones produced by the adrenal glands, other thyroid disorder, overactive adrenal gland activity, inflammation of the pituitary gland situated at the base of the brain
- abnormal lipoprotein in the blood
- inflammation of the brain, neurotoxicity, motion sickness, motor dysfunction
- blurred vision
- disease of heart muscle, a reduction in blood flow to the heart muscle (myocardial ischaemia), tissue myocardial ischaemia, a collection of fluid in the pericardium, increased level of myocardial necrosis marker
- dry mouth, inflammation of the stomach, gingival bleeding
- thickened, sometimes scaly, skin growth, changes in skin colour, dry skin
- auto-inflammation of the muscles (autoimmune myositis), inflammation of the joint
- chills

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- inflammation of the muscles (myositis)

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

5. How to store Hetronifly

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

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

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, the diluted solution has been demonstrated to be stable for 24 hours in a refrigerator (2°C to 8°C), which may include up to 6 hours at room temperature (at or below 25°C).

Do not use this medicine if you notice visible particles.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will dispose any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Hetronifly contains
The active substance is serplulimab.

Each ml of concentrate contains 10 mg of serplulimab. One vial of 10 ml contains 100 mg of serplulimab.

The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride (See section 2: Hetronifly contains sodium), mannitol, polysorbate 80, water for injections.

What Hetronifly looks like and contents of the pack
Hetronifly is a concentrate for solution for intravenous infusion, which is supplied in a glass vial with a rubber stopper. The vial contains 10 mg/ml of serplulimab. The concentrate is a colourless to slightly yellow, clear to slightly opalescent liquid. Each carton contains 1 vial.

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Manufacturer
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Accord Healthcare Single Member S.A.,
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This leaflet was last revised in

Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Preparation and administration of the infusion
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 the visible particle is observed.
- Confirm the dose of the product and calculate the required volume of Hetronifly.
- Withdraw a volume of the 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. 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.
- 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.