# EU Risk Management Plan for HETRONIFLY (Serplulimab)

**RMP version to be assessed as part of this application:**

RMP Version number: 3.0

Data lock point for this RMP: 21Mar2025

Date of final sign-off: 12May2026

**Rationale for submitting an updated RMP:**

Addition of a new indication for serplulimab, in combination with carboplatin and nab-paclitaxel is indicated for the first-line treatment of adult patients with unresectable locally advanced or metastatic squamous non-small cell lung carcinoma.

**Summary of significant changes in this RMP:**

Addition of study HLX10-004-NSCLC303 in Module SI, Module SIII, Module SVII.

**Other RMP versions under evaluation:** None

**Details of the currently approved RMP:**

Version number: 1.0

Approved with procedure: EMEA/H/C/006170/0006

Date of approval (Opinion date): 19Sep2024

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**QPPV Name:** [redacted]

[redacted]

[redacted]

**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

# Table of Content

# List of Abbreviations

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|---|---|
| ALT | Alanine transaminase |
| AST | Aspartic transaminase |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CNS | Central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| Cr | Creatinine |
| CTCAE | Common terminology criteria for adverse events |
| CTLA4 | Cytotoxic T lymphocyte associated antigen-4 |
| CYP | Cytochrome P450 |
| DLP | Data lock point |
| EM | Educational material |
| EPAR | European public assessment report |
| ES | Extensive-stage |
| ESMO | European society for medical oncology |
| GMP | Good manufacturing practices |
| HCP | Healthcare professional |
| HIV | Human immunodeficiency virus |
| ICH | International council for harmonisation of technical requirements for pharmaceuticals for human use |
| ICI | Immune checkpoint inhibitor |
| irAE | Immune-related adverse event |
| LUAD | Lung adenocarcinoma |
| LVEF | Left ventricular ejection fraction |
| NCCN | National comprehensive cancer network |
| NCI | National cancer institute |
| NK | Natural killer |
| NOAEL | No observed adverse effect level |
| NSCLC | Non-small cell lung carcinoma |
| NYHA | New York heart association |
| OS | Overall survival |
| OSCC | Oesophageal squamous cell carcinoma |
| PD-1 | Programmed cell death-1 |
| PD-L1 | Programmed cell death-ligand 1 |
| PD-L2 | Programmed cell death-ligand 2 |
| PFS | Progression-free survival |
| PSUR | Periodic safety update report |
| PT | (MedDRA) Preferred term |
| SCLC | Small cell lung cancer |
| SmPC | Summary of product characteristics |
| SOC | (MedDRA) System organ class |
| TBIL | Total bilirubin |
| Tregs | Regulatory T cells |
| ULN | Upper limit of normal |
| US | United States |

# Part I: Product Overview

| | |
|---|---|
| **Active substance(s)**<br><br>**(INN or common name)** | Serplulimab |
| **Pharmacotherapeutic group(s) (ATC Code)** | L01FF12 |
| **Marketing Authorisation Holder** | Accord Healthcare S.L.U.<br><br>World Trade Center, Moll de Barcelona, s/n<br><br>Edifici Est, 6a Planta<br><br>08039 Barcelona<br><br>Spain |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name in the European Economic Area (EEA)** | HETRONIFLY 10 mg/ml concentrate for solution for infusion |
| **Marketing authorisation procedure** | Centralised Procedure |
| **Brief description of the product** | Chemical class: Recombinant Humanised Anti-PD-1 Monoclonal Antibody |
| | Summary of mode of action:<br><br>Serplulimab is a humanised monoclonal IgG4 antibody which binds to the 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. |
| | Important information about its composition:<br><br>Serplulimab is a humanised IgG4 monoclonal antibody. It is composed of two light chains and two heavy chains, with 214 amino acids in each light chain and 443 amino acids in each heavy chain. The molecular weight without N-linked glycosylation is around 144 kDa. It is produced in CHO cells and is manufactured in GMP facilities. |

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| | The pharmaceutical form is concentrate for solution for infusion. The intended route of administration is intravenous use. The appearance of the product is colourless to slightly yellow, clear to slightly opalescent solution. The product is supplied as a sterile liquid solution with a concentration of 10.0 mg/ml (100 mg/vial) filled in a 10 ml Type I clear glass vial. The excipients include [redacted] mg/ml citric acid monohydrate, [redacted] mg/ml sodium citrate, [redacted] mg/ml sodium chloride, [redacted] mg/ml mannitol, [redacted] mg/ml polysorbate 80 and water for injections. The final pH value is adjusted to [redacted] ±0.3. The product should be stored at 2-8°C, protected from light, and should not be frozen. |
| **Hyperlink to the Product Information** | HETRONIFLY Product Information (Module 1.3.1) |
| **Indications in the EEA** | Current:<br><br>Small cell lung cancer (SCLC)<br><br>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).<br><br>Non-small cell lung carcinoma (NSCLC)<br><br>HETRONIFLY in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult non-squamous NSCLC patients with no EGFR, ALK or ROS1 positive mutations and who have:<br><br>• locally advanced NSCLC who are not candidates for surgery or radiotherapy, or<br><br>• metastatic NSCLC.<br><br>HETRONIFLY in combination with carboplatin and nab-paclitaxel is indicated for the first-line treatment of adult patients with unresectable locally advanced or metastatic squamous non-small cell lung carcinoma.<br><br>Oesophageal squamous cell carcinoma (OSCC)<br><br>HETRONIFLY in combination with fluoropyrimidine- and platinum-based chemotherapy is indicated for the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5. |
| | Proposed:<br><br>Not applicable. |
| **Dosage in the EEA** | Current: |

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| | SCLC or NSCLC: The recommended dose in both the induction and maintenance phases is 4.5 mg/kg bodyweight serplulimab every 3 weeks until disease progression or unacceptable toxicity.<br><br>OSCC: The recommended dose in both the induction and maintenance phases is 3.0 mg/kg bodyweight serplulimab every 2 weeks until disease progression or unacceptable toxicity. |
| | Proposed:<br><br>Not applicable. |
| **Pharmaceutical form and strengths** | Current:<br><br>10 mg/ml concentrate for solution for infusion |
| | Proposed:<br><br>Not applicable. |
| **Is the product subject to additional monitoring in the EU?** | Yes |

# Part II: Safety specification

# Part II: Module SI - Epidemiology of the indication(s) and target population(s)

**Indication: extensive-stage small cell lung cancer (ES-SCLC)**

- **Incidence and Prevalence:**

  SCLC is an aggressive type of cancer derived from epithelial cells with neuroendocrine differentiation. It accounts for 15%-20% of the total number of lung cancer cases (Eskandar 2015). Most patients present with tumour metastases as the first symptom (Klautke 2008). Only 30% to 40% of patients are in the limited stage at the time of initial diagnosis, while the majority of patients are already in the extensive stage of the disease (Kurup 2004). Patients with extensive disease have a short duration of survival on supportive care only due to extensive tumour metastasis and poor physical status. Until recently, the first-line treatment for metastatic SCLC consisted of the combination chemotherapy of a platinum and etoposide, with an estimated median overall survival (OS) of 9 to 10 months and 1-year OS of approximately 35%, although most patients relapse within 6 months (ESMO Clinical Practice Guidelines 2021). With a combination of surgery, radiotherapy, and chemotherapy, the median survival of patients with ES-SCLC can reach 8 to 13 months, with a 2-year survival rate of 5% (Puglisi 2010).

- **Demographics of the population in the ES-SCLC indication – age, gender, racial and/or ethnic origin and risk factors for the disease:**

  Lung cancer, including all histological subtypes, is more prevalent in high-income countries/regions, reflecting relative levels of tobacco consumption. SCLC is most prevalent in men but the proportion of cases in women compared to men has risen worldwide over the past 50 years, again reflecting tobacco consumption trends. Studies suggest possible links between exposure to air pollution and to radon and SCLC in never-smokers but evidence for both is limited. Inherited genetic factors are thought to play a minor role in the susceptibility to developing SCLC. Genetic variation does contribute to risk of nicotine addiction and might thereby indirectly influence SCLC risk (Charles 2021).

- **The main existing treatment options:**

  Atezolizumab and durvalumab have been approved for first-line treatment of ES-SCLC in combination with carboplatin (or cisplatin for durvalumab) and etoposide in the United States (US) and in the European Union. The current National Comprehensive Cancer Network (NCCN) guidelines and the European Society for Medical Oncology (ESMO) guidelines both recommend atezolizumab or durvalumab in combination with the chemotherapy regimen of a platinum plus etoposide for first-line treatment of ES-SCLC (NCCN Clinical Practice Guidelines 2023, ESMO Clinical Practice Guidelines 2021).

- **Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

  With an estimated 2.2 million new cancer cases and 1.8 million deaths, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer

death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in 5 (18.0%) deaths (Hyuna 2021). SCLC represents about 15% of all lung cancers and is marked by an exceptionally high proliferative rate, strong predilection for early metastasis and poor prognosis. SCLC comprises an estimated 250 000 new cases and at least 200 000 deaths globally each year. The specific incidence of SCLC in different countries/regions or continents is not well described (Charles 2021).

- **Important co-morbidities:**

  Comorbidity type of SCLC included cerebrovascular disease, diabetes mellitus, other malignancy, pulmonary disease, cardiac disease, vascular disease, hypertension and digestive disease. The presence of comorbidity among patients with SCLC is very common and has been increasing. Multimorbidity affected survival in those with extensive-stage SCLC owing to differences in treatment. More specifically, digestive (limited-stage), cardiac (limited- and extensive-stage), and cerebrovascular (extensive-stage) disease affected the prognosis (Mieke 2015).

**Indication: non-squamous NSCLC**

- **Incidence and Prevalence:**

  Non-squamous NSCLC accounts for about 75% of NSCLC, including adenocarcinoma, large cell carcinoma, and other subtypes, with adenocarcinoma being the most common (Davidson 2013). According to the estimate for 2022, adenocarcinoma is the most common lung cancer subtype worldwide. Of the estimated 2 480 675 new lung cancer cases worldwide, adenocarcinoma accounting for 50.8% (1 259 182 cases), followed by squamous NSCLC at 24.9% (616 769 cases), small-cell carcinoma at 10.8% (267 965 cases), and large-cell carcinoma at 6.5% (161 132 cases) (Luo 2025).

- **Demographics of the population in the non-squamous NSCLC indication – age, gender, racial and/or ethnic origin and risk factors for the disease:**

  While non-squamous NSCLC is more prevalent in men, the incidence of adenocarcinoma has risen significantly among women in recent years. In 2022, adenocarcinoma accounted for 45.6% (717 211 cases) of male lung cancers and 59.7% (541 971 cases) of female lung cancers, while large-cell carcinoma represented 6.5% in both genders (101 861 cases in men and 9 271 in women) (Luo 2025). East Asia exhibits the highest age-standardized incidence rates of adenocarcinoma globally (Bray 2024). Although smoking remains the primary risk factor, 20–30% of non-squamous NSCLC cases occur in lifelong non-smokers, particularly East Asian women, who are strongly associated with oncogenic EGFR mutations and chronic exposure to indoor air pollutants like cooking oil fumes (Fidler-Benaoudia 2020). Additionally, a novel mechanism has been proposed on the underlying means by which air pollution causes adenocarcinoma (Hill 2023).

- **The main existing treatment options:**

  In patients with driver gene-negative non-squamous NSCLC, pembrolizumab monotherapy (for PD-L1 ≥50%), pembrolizumab combined with platinum-based chemotherapy and pemetrexed (for PD-L1 ≥1%), and atezolizumab combined with bevacizumab plus chemotherapy (carboplatin + paclitaxel) are recommended as

first-line treatments by NCCN (Ettinger 2021) and ESMO (Hendriks 2023) guidelines. Dual immunotherapy (e.g., nivolumab plus ipilimumab with abbreviated chemotherapy) is also recommended in certain circumstances, such as rapid tumour burden reduction in PD-L1 ≥1% patients.

- **Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

  Lung adenocarcinoma (LUAD) is the most common subtype of non-squamous NSCLC, and accounts for over half of all lung cancer patients. LUAD requires individualized treatment based on tumour progression; early-stage LUAD is mainly treated surgically, whereas advanced-stage and metastatic patients require systemic therapy (Kris 2017). However, anti-tumour efficiency in LUAD patients is usually limited by chemotherapy resistance and apoptotic escape, leading to tumour recurrence and a poor prognosis. The 5-year survival of metastatic LUAD patients is lower than 20% (Shu 2023).

- **Important co-morbidities:**

  Lung cancer patients commonly have comorbid conditions, including chronic obstructive pulmonary disease (COPD), diabetes, congestive heart failure, cerebrovascular disease, and peripheral vascular disease. The high prevalence of these comorbidities is strongly associated with smoking and aging (Hernandez 2023).

**Indication: Oesophageal squamous cell carcinoma (OSCC)**

- **Incidence and Prevalence:**

  Oesophageal cancer ranks as the 11th most commonly diagnosed cancer and the seventh leading cause of cancer-related deaths worldwide. In 2022, an estimated 511 000 new cases and 445 000 deaths were reported, with age-standardized incidence and mortality rates of 5.0 and 4.3 per 100 000, respectively (Bray 2024). The estimated number of oesophageal cancer prevalent cases (5-year) was 717 169, both sexes, with the majority (75.1%, 538 504 cases) occurring in Asia, followed by Europe at 10.0% (71 996 cases) (https://gco.iarc.who.int/en). OSCC and oesophageal adenocarcinoma are the two main oesophageal cancer histological subtypes that have distinct epidemiological and clinical features. Globally, OSCC is the most common oesophageal cancer subtype, which accounts for 80% of oesophageal cancer cases (Sheikh 2023).

- **Demographics of the population in the OSCC indication – age, gender, racial and/or ethnic origin and risk factors for the disease:**

  There remains a two-fold to three-fold difference in incidence and mortality rates between the sexes, with rates somewhat greater in high/very high Human Development Index (HDI) versus medium/low HDI countries among men, but the inverse among women. The highest rates are seen in Eastern Asia and Eastern Africa, where Malawi has the highest incidence rates worldwide in both men and women (Bray 2024). The geographic variations in oesophageal cancer incidence substantially vary between the two most common histologic subtypes (OSCC and oesophageal adenocarcinoma), which have quite different etiologies. In higher HDI settings, smoking and alcohol are major risk factors for squamous cell carcinoma;

whereas, in lower HDI settings, the risk factors are yet to be uncovered (Bray 2024).

- **The main existing treatment options:**

  OSCC poses a major challenge for clinicians as the prognosis is poor and treatment options are limited. However, recent advances in immunotherapy have significantly changed the treatment algorithm of OSCC. FDA had approved combination therapies with either pembrolizumab + chemotherapy, nivolumab + chemotherapy or nivolumab + ipilimumab are possible options for the first-line treatment of advanced OSCC independent of PD-L1 expression (Shoji 2024). The EMA was more restrictive choosing to approve the pembrolizumab only for CPS ≥10 and nivolumab or nivolumab + ipilimumab only for TPS ≥1% patients (Puhr 2023).

- **Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

  Surgery remains the mainstay of treatment for OSCC, although surgery alone achieves poor locoregional control and poor long-term outcome. The 5-year survival rate for non-metastatic OSCC is 10–40% if treated with surgery alone. Unfortunately, esophagectomy itself is a complex procedure with significant morbidity and mortality. Two percent to 25% of patients die within 30 days after surgery (Liu 2016). Unfortunately, chemotherapy alone can lead to poor survival, equating to median OS of 7–13 months as well as a less than 20% 5-year OS (Zhang 2023).

- **Important co-morbidities:**

  Patients often present with nonspecific early symptoms and by the time typical symptoms such as dysphagia, coughing, and pain manifest, the disease is frequently in an advanced stage. Given the high metabolic demands imposed by OSCC and its associated symptoms which adversely affect food intake, patients often experience malnutrition (Chen 2024).

**Indication: squamous NSCLC**

- **Incidence and Prevalence:**

  Lung cancer is the leading cause of global cancer incidence and mortality in 2022, with an estimated 2.48 million new cases and 1.82 million deaths worldwide (Bray 2024). NSCLC constitutes approximately 80% of all lung cancers, with the squamous subtype representing 20%–30%, making it the second most common histologic subtype after adenocarcinoma (Lau 2022). Among the estimated 2 480 675 new cases of lung cancer worldwide, 616 769 (24.86%) were squamous NSCLC (Luo 2025). The 5-year prevalence of lung cancer worldwide was 3 221 461 cases, with 610 169 (18.9%) in Europe, 2 058 202 (63.9%) in Asia, and 325 855 (10.1%) in Northern America (https://gco.iarc.who.int/en)

- **Demographics of the population in the squamous NSCLC indication –age, gender, racial and/or ethnic origin and risk factors for the disease:**

  The incidence of squamous NSCLC is higher in males than in females. In 2022, squamous NSCLC accounted for 29.4% (461 171 cases) of new lung cancer cases among males and 17.1% (155 598 cases) among females worldwide. The highest age-standardized rates for squamous NSCLC were observed in Eastern Europe

among males (21.70 per 100 000) and in North America among females (5.28 per 100 000) (Luo 2025). Squamous NSCLC is connected with smoking more than any other kind of NSCLC and is characterized by recurring somatically altered genes and pathways linked to smoking (Lahiri 2023).

- **The main existing treatment options:**

  Individuals with NSCLC often present with locally advanced stage III disease not suitable for resection or curative intent chemoradiotherapy, or with advanced stage IV disease historically associated with a poor 5-year survival rate (7%) (O'Byrne 2023). Current NCCN (Ettinger 2021) and ESMO (Hendriks 2023) guidelines recommend pembrolizumab combined with carboplatin/paclitaxel or nab-paclitaxel as the preferred first-line regimen for eligible metastatic squamous NSCLC patients. This recommendation is supported by robust clinical trial data demonstrating survival benefits. Additional suitable options include nivolumab/ipilimumab dual immunotherapy or nivolumab/ipilimumab combined with paclitaxel/carboplatin, which may be considered for specific clinical scenarios, such as high tumour burden.

- **Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

  In 2022, lung cancer caused more than 1.8 million deaths worldwide, which is more than twice the number of deaths caused by colorectal cancer, the second most common cause of cancer mortality (Bray 2024). Geographically, 1 142 397 (62.9%) of these deaths occurred in Asia, 375 569 (20.7%) in Europe, and 150 675 (8.3%) in Northern America. Despite advances in surgery, chemotherapy, radiotherapy, and targeted therapy, squamous NSCLC remains challenging to treat. Over 60% of stage I/II patients relapse and die within 5 years post-surgery, while 75% are diagnosed at advanced stages (III/IV), with only 5% surviving 5 years. These statistics underscore the urgent need for improved therapeutic strategies (Wang 2022).

- **Important co-morbidities:**

  Squamous NSCLC is strongly associated with advanced age and heavy smoking, which explains the higher prevalence of smoking- and age-related comorbidities in these patients compared to other lung cancer subtypes. Chronic obstructive pulmonary disease and cardiovascular disease are the most common comorbid conditions among these patients (Socinski 2016).

# Part II: Module SII - Non-clinical part of the safety specification

Weekly treatment at 100 mg/kg for 13-week or 31-week in *cynomolgus* monkeys resulted in some immune-mediated adverse effects. However, serplulimab was well tolerated with no appreciable adverse effects at both 5 and 50 mg/kg, and the no observed adverse effect level (NOAEL) is considered to be 50 mg/kg under the study conditions.

The key safety findings from the non-clinical program and their relevance to clinical use in humans are presented in **Table 1**.

**Table 1 Key safety findings from non-clinical studies and relevance to human usage**

| **Key Safety findings (From non-clinical studies)** | **Relevance to human usage** |
|---|---|
| **Toxicity:** | |
| **Repeat-dose toxicity:**<br>**Death**<br>*13-week repeat-dose toxicity:*<br>At 100 mg/kg, one female animal was moribund and euthanized for amoeba-related diarrhoea, and the immune-related adverse effect cannot be ruled out for exacerbating or causing the infection. Another female animal at 100 mg/kg died due to the treatment-related anaphylactic reactions.<br>*31-week repeat-dose toxicity:*<br>At 50 mg/kg, one female animal died with severe alveolar haemorrhage secondary to individual specific anaphylactic reactions.<br>**Gastrointestinal system**<br>*13-week or 31-week repeat-dose toxicity:*<br>At 0, 5, 50 or 100 mg/kg, the soft stools and/or loose stools were observed in animals with moderate incidence. | Diarrhoea in preclinical species is relevant to humans.<br>Immunogenicity-related anaphylactic reactions in preclinical species are not predictive for humans.<br>Treatment-emergent infusion reactions were noted in human usage. |
| **Reproductive and developmental toxicity**<br>In the 31-week repeat-dose toxicity study, pharmacology-related minimal mononuclear cell infiltrate around blood vessels and within the interstitium of the epididymidis were noted.<br>No others treatment-related histopathological changes in male and female reproductive system, were noted in the 13-week and 31-week repeat-dose toxicity study in | Based on the mechanism of action and published literature, serplulimab may cause harm to the foetus.<br>Women of childbearing potential should be advised to use effective methods of contraception and avoid pregnancy while taking serplulimab and for at least 6 months after the last dose. |

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| cynomolgus monkeys. However, not all animals were sexually mature in these studies. | |
| **Genotoxicity**<br><br>Genotoxicity studies have not been conducted with serplulimab since the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals (ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals, 2011). | Not applicable. |
| **Carcinogenicity**<br><br>Carcinogenicity studies have not been conducted with serplulimab since they are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH guideline S9 nonclinical evaluation for anticancer pharmaceuticals, 2010). | Not applicable. |
| **Cardiovascular, nervous and respiratory Systems**<br><br>Moderate spinal cord gliosis and neuropil degeneration (one female monkey), and minimal to slight perivascular mononuclear inflammation in brain choroid plexus were observed at the microscopic examination in the 13-week or 31-week repeat-dose toxicity study, respectively. | Based on mechanism of action and nonclinical data, inflammation in brain may be noted in clinical studies. |
| **Mechanisms for drug interactions**<br><br>No studies were conducted in line with ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals, 2011. | The potential for drug-drug interaction between serplulimab and small molecule drug products is very low, given that serplulimab is a therapeutic monoclonal antibody and is expected to be degraded into amino acids via catabolism; therefore, it is unlikely to influence drug metabolizing enzymes or transporters. |
| **Other toxicity related information or data**<br><br>None | Not applicable. |

# Part II: Module SIII - Clinical trial exposure

The pooled safety data set included the safety data in 10 clinical trials with serplulimab.

Serplulimab in pivotal study HLX10-005-SCLC301 for ES-SCLC

Clinical trial exposure data pertaining to the ES-SCLC population (patient: 389) included patients who received serplulimab at 4.5 mg/kg every 3 weeks in combination with carboplatin and etoposide in the pivotal study.

Serplulimab in pivotal study HLX10-002-NSCLC301 for non-squamous NSCLC

Clinical trial exposure data pertaining to the non-squamous NSCLC population (patient: 503) included patients who received serplulimab at 4.5 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 (recombinant anti-VEGF humanised monoclonal antibody injection) in the pivotal study.

Serplulimab in pivotal study HLX10-007-EC301 for OSCC

Clinical trial exposure data pertaining to the OSCC population (patient: 382) included patients who received serplulimab at 3.0 mg/kg every 2 weeks in combination with cisplatin and 5-FU in the pivotal study.

Serplulimab in pivotal study HLX10-004-NSCLC303 for squamous NSCLC

Clinical trial exposure data pertaining to the squamous NSCLC population (patient: 455) included patients who received serplulimab at 4.5 mg/kg every 3 weeks, monotherapy or in combination with carboplatin and nab-paclitaxel in the pivotal study.

Serplulimab Single-Agent (pivotal studies not included)

The integrated safety analyses supporting this RMP included patients who were administered at 0.3 mg/kg (patient: 3), 1 mg/kg (patient: 4), 3 mg/kg (patient: 6) and 10 mg/kg (patient: 16) of serplulimab every 2 weeks, at 200 mg every 2 weeks (patient: 9), 300 mg every 3 weeks (patient: 9), 400 mg every 4 weeks (patient: 10) and 600 mg every 6 weeks (patient: 9) in clinical trial HLX10-001; at 3 mg/kg of serplulimab every 2 weeks in clinical trials HLX10-010-MSI201 (patient: 108) and HLX10-008-HCC201 (patient: 21).

Serplulimab in combination with chemotherapy (pivotal studies not included)

The integrated safety analyses supporting this RMP included patients who were administered at 4.5 mg/kg of serplulimab every 3 weeks in clinical trial HLX10-011-CC201 (patient: 21).

Serplulimab in combination with other monoclonal antibodies (pivotal studies not included)

The integrated safety analyses supporting this RMP included patients who were administered at 1 mg/kg (patient: 3), 3 mg/kg (patient: 3) and 10 mg/kg (patient: 20) of serplulimab every 2 weeks in clinical trial HLX10HLX04-001; at 3 mg/kg of serplulimab every 2 weeks in clinical trial HLX10-008-HCC201 (patient: 102); at 3 mg/kg of serplulimab every 2 weeks in clinical trial HLX10HLX07-001 (patient: 13).

The total number of patients treated with serplulimab across 10 clinical trials ('Pooled Safety Set') is 2 086. **Table 2** provides the overview of 10 clinical trials of serplulimab pooled in safety evaluations.

**Table 2: Overview of 10 Clinical Trials of Serplulimab Pooled in Safety Evaluations**

| Study No. | Title | Study Treatment | Control | Serplulimab Dose | No. of Subjects in Analysis | Study Status | Cutoff Date for Safety Data |
|---|---|---|---|---|---|---|---|
| HLX10-002-NSCLC301 (Pivotal study for non-squamous NSCLC) | A Three-Arm, Randomized, Double-blind, Multicentre, Phase III Clinical Study to Evaluate HLX10 (Recombinant Humanised Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin- Pemetrexed) Versus HLX10 + HLX04 (Recombinant Anti-VEGF Humanised Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Pemetrexed) Versus Chemotherapy (Carboplatin- Pemetrexed) as First-Line Treatment of Advanced Non-Squamous Non-Small Cell Lung Cancer | Serplulimab with carboplatin-pemetrexed or Serplulimab plus HLX04 with carboplatin-pemetrexed | Placebo with carboplatin-pemetrexed | 4.5 mg/kg, Q3W | Stage I:<br>Serplulimab + HLX04+chemotherapy: 6;<br><br>Stage II:<br>Serplulimab+ chemotherapy: 214;<br>Serplulimab+ HLX04+chemotherapy: 211;<br>Placebo + chemotherapy switching to Serplulimab+ HLX04: 72;<br><br>Total: 503 | Ongoing | 15Jun2023 |
| HLX10-007-EC301 (Pivotal study for OSCC) | A Randomized, Double-Blind, Multicentre, Phase III Clinical Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) Versus Placebo in Combination with Chemotherapy (Cisplatin + 5-FU) as First-Line Therapy in Patients with Locally Advanced/Metastatic Oesophageal Squamous Cell Carcinoma | Serplulimab with cisplatin and 5-FU combination therapy | Placebo with cisplatin and 5-FU | 3 mg/kg, Q2W | 382 | Completed | 09Jan2023 |

| Study No. | Title | Study Treatment | Control | Serplulimab Dose | No. of Subjects in Analysis | Study Status | Cutoff Date for Safety Data |
|---|---|---|---|---|---|---|---|
| HLX10-005-SCLC301<br>(Pivotal trial for ES-SCLC) | A Randomised, Double-Blind, Multicentre, Phase III Study to Evaluate HLX10 in Combination with Chemotherapy (Carboplatin-Etoposide) in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC) | Serplulimab with carboplatin and etoposide combination therapy | Placebo with carboplatin and etoposide | 4.5 mg/kg, Q3W | 389 | Completed | 07May2024 |
| HLX10-001 | A Prospective Open-label Dose-Escalation Phase I Study to Investigate the Safety and Tolerability, and to Determine the Maximum Tolerated Dose and Recommended Phase II Dose, of HLX10 in Patients with Advanced Solid Tumours | Serplulimab monotherapy | None | 0.3 mg/kg Q2W,<br>1 mg/kg Q2W,<br>3 mg/kg Q2W,<br>10 mg/kg Q2W<br>200 mg Q2W,<br>300 mg Q3W,<br>400 mg Q4W<br>600 mg Q6W | 3<br>4<br>6<br>16<br>9<br>9<br>10<br>9<br>Total: 66 | Completed | 05Jan2024 |
| HLX10-010-MSI201 | A Single-arm, Multi-centre, Phase II Clinical Study to Evaluate the HLX10 Monotherapy for the Treatment of Unresectable or Metastatic Microsatellite Instability-high (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumours That Failed to Respond to Standard Therapy | Serplulimab monotherapy | None | 3 mg/kg, Q2W | 108 | Completed | 10Jul2021 |

| Study No. | Title | Study Treatment | Control | Serplulimab Dose | No. of Subjects in Analysis | Study Status | Cutoff Date for Safety Data |
|---|---|---|---|---|---|---|---|
| HLX10-008-HCC201 | A Single-arm, Open, Multicentre, Phase II Clinical Study Evaluating the Use of HLX10 (Recombinant Anti-PD-1 Humanised Monoclonal Antibody Injection) in Combination with HLX04 (Recombinant Anti-VEGF Humanised Monoclonal Antibody Injection) for the Treatment of Advanced Hepatocellular Carcinoma (HCC) Patients | Serplulimab monotherapy or Serplulimab with HLX04 combination therapy | None | 3 mg/kg, Q2W | Monotherapy : 21<br>Combination therapy: 102<br>Total: 123 | Completed | 07Feb2023 |
| HLX10-004-NSCLC303<br>(Pivotal study for squamous NSCLC) | A Randomised, Double-Blind, Multicentre, Phase III Clinical Study of HLX10 + Chemotherapy (Carboplatin-Nanoparticle Albumin-Bound (Nab)-Paclitaxel) vs. Placebo + Chemotherapy (Carboplatin-Nab-Paclitaxel) as First-Line Therapy for Locally Advanced or Metastatic Squamous NSCLC | Serplulimab with carboplatin and nab-paclitaxel combination therapy | Placebo with carboplatin and nab-paclitaxel | 4.5 mg/kg, Q3W | 358/455[a] | Completed | 31Jan2023 |
| HLX10-011-CC201 | A Single-Arm, Open-Label, Multicentre, Phase II Clinical Study to Evaluate Efficacy and Safety of HLX10 (Recombinant Humanised Anti-PD-1 Monoclonal Antibody Injection) Combined with Albumin-Bound Paclitaxel in Patients with Advanced Cervical Cancer Who Have Progressive Disease or Intolerable Toxicity After First-Line Standard Chemotherapy | Serplulimab with paclitaxel combination therapy | None | 4.5 mg/kg, Q3W | 21 | Completed | 22Sep2022 |

| Study No. | Title | Study Treatment | Control | Serplulimab Dose | No. of Subjects in Analysis | Study Status | Cutoff Date for Safety Data |
|---|---|---|---|---|---|---|---|
| HLX10HLX04-001 | A Phase I Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Recombinant Anti-PD-1 Humanised Monoclonal Antibody Injection (HLX10) in Combination with Recombinant Anti-VEGF Humanised Monoclonal Antibody Injection (HLX04) in Patients with Advanced Solid Tumours | Serplulimab with HLX04 combination therapy | None | 1 mg/kg Q2W,<br>3 mg/kg Q2W,<br>10 mg/kg Q2W | 3<br>3<br>20<br>Total: 26 | Completed | 11Oct2022 |
| HLX10HLX07-001 | A Multiple-centre, Open-label, Phase II clinical trial to Evaluate the Efficacy and Safety of HLX10 in Combination with HLX07 in Patients with Advanced Head and Neck Tumours | Serplulimab with HLX07 combination therapy | None | 3 mg/kg, Q2W | 13 | Completed | 16Sep2022 |

Abbreviations: Q2W=once every 2 weeks, Q3W=once every 3 weeks, Q4W=once every 4 weeks, Q6W=once every 6 weeks.

[a] In the HLX10-004-NSCLC303 study, subjects randomised to the placebo group either ended treatment or were allowed to crossover to receive serplulimab after the first progressive disease. As of the cutoff date, 97 subjects in the placebo group crossed over to receive serplulimab monotherapy. Therefore, 455 subjects received serplulimab (serplulimab + chemotherapy 358 subjects, serplulimab monotherapy 97 subjects).

The clinical trial exposure analyses include clinical exposure by time, age and gender, and racial origin.

**Table SIII.1-A** summarises the duration of exposure to serplulimab in the pivotal studies of HLX10-005-SCLC301, HLX10-002-NSCLC301, HLX10-007-EC301 and HLX10-004-NSCLC303, and in the Pooled Safety Set, respectively. Overall, the mean number of months on treatment was 8.68 (range: 0 to 52.7 months).

**Table SIII.1-A.1 : Summary of Drug Exposure in Pivotal Studies**

| | HLX10-005-SCLC301 (N=389) | HLX10-002-NSCLC301 (N=503) | HLX10-007-EC301 (N=382) | HLX10-004-NSCLC303 (N=455) | Total Population (N=2086) |
|---|---|---|---|---|---|
| Treatment Duration (months) | | | | | |
| N | 389 | 503 | 382 | 455 | 2086 |
| Mean +/- SD | [redacted] | [redacted] | [redacted] | [redacted] | 8.68 +/- 8.910 |
| Median | [redacted] | [redacted] | [redacted] | [redacted] | 5.55 |
| Q1, Q3 | [redacted] | [redacted] | [redacted] | [redacted] | 2.43, 12.42 |
| Min, Max | [redacted] | [redacted] | [redacted] | [redacted] | 0.0, 52.7 |

**Table SIII.1-A.2 : Summary of Drug Exposure in Pooled Safety Set**

| | <RP2D/3D | | | ≥RP2D/3D | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monotherapy (N=7) | Other Combination (N=3) | Total (N=10) | Monotherapy (N=285) | Chemotherapy Combination (N=1364) | Other Combination (N=427) | Total (N=2076) | Total Population (N=2086) |
| Treatment Duration (months) | | | | | | | | |
| N | 7 | 3 | 10 | 285 | 1364 | 427 | 2076 | 2086 |
| Mean +/- SD | 2.05 +/- 1.867 | 8.47 +/- 2.957 | 3.97 +/- 3.726 | 5.73 +/- 6.736 | 9.34 +/- 9.498 | 8.63 +/- 7.851 | 8.70 +/- 8.922 | 8.68 +/- 8.910 |
| Median | 1.41 | 9.69 | 3.06 | 2.79 | 6.00 | 6.28 | 5.55 | 5.55 |
| Q1, Q3 | 0.49, 3.25 | 5.09, 10.61 | 0.95, 5.32 | 0.99, 8.28 | 3.27, 12.68 | 2.10, 13.17 | 2.45, 12.45 | 2.43, 12.42 |
| Min, Max | 0.0, 5.3 | 5.1, 10.6 | 0.0, 10.6 | 0.0, 30.2 | 0.0, 52.7 | 0.0, 34.1 | 0.0, 52.7 | 0.0, 52.7 |

**Table SIII.1-B** presents the duration of exposure to serplulimab over time in the pivotal studies of HLX10-005-SCLC301, HLX10-002-NSCLC301, HLX10-007-EC301 and HLX10-004-NSCLC303, and in the Pooled Safety Set, respectively. Overall, 1 475 patients were treated for ≥ 3 months in which 994 patients were treated for ≥ 6 months, 537 patients for ≥ 12 months in the clinical programmes.

**Table SIII.1-B.1：Duration of Exposure in Pivotal Studies**

| | HLX10-005-SCLC301 (N=389) | HLX10-002-NSCLC301 (N=503) | HLX10-007-EC301 (N=382) | HLX10-004-NSCLC303 (N=455) | Total Population (N=2086) |
|---|---|---|---|---|---|
| Treatment Duration | | | | | |
| <3 Months | [redacted] | [redacted] | [redacted] | [redacted] | 611 (29.3%) |
| >=3 Months | [redacted] | [redacted] | [redacted] | [redacted] | 1475 (70.7%) |
| >=6 Months | [redacted] | [redacted] | [redacted] | [redacted] | 994 (47.7%) |
| >=12 months | [redacted] | [redacted] | [redacted] | [redacted] | 537 (25.7%) |
| Total | 389 (100%) | 503 (100%) | 382 (100%) | 455 (100%) | 2086 (100%) |
| Person-time exposure (year) | | | | | |
| <3 Months | [redacted] | [redacted] | [redacted] | [redacted] | 65.98 |
| >=3 Months | [redacted] | [redacted] | [redacted] | [redacted] | 1442.90 |
| >=6 Months | [redacted] | [redacted] | [redacted] | [redacted] | 1270.11 |
| >=12 months | [redacted] | [redacted] | [redacted] | [redacted] | 952.51 |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | 1508.88 |

**Table SIII.1-B.2: Duration of Exposure in Pooled Safety Set**

| | <RP2D/3D | | | ≥RP2D/3D | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monotherapy (N=7) | Other Combination (N=3) | Total (N=10) | Monotherapy (N=285) | Chemotherapy Combination (N=1364) | Other Combination (N=427) | Total (N=2076) | Total Population (N=2086) |
| Treatment Duration | | | | | | | | |
| <3 Months | 5 (71.4%) | 0 | 5 (50.0%) | 152 (53.3%) | 321 (23.5%) | 133 (31.1%) | 606 (29.2%) | 611 (29.3%) |
| >=3 Months | 2 (28.6%) | 3(100%) | 5 (50.0%) | 133 (46.7%) | 1043 (76.5%) | 294 (68.9%) | 1470 (70.8%) | 1475 (70.7%) |
| >=6 Months | 0 | 2 (66.7%) | 2 (20.0%) | 90 (31.6%) | 682 (50.0%) | 220 (51.5%) | 992 (47.8%) | 994 (47.7%) |
| >=12 months | 0 | 0 | 0 | 51 (17.9%) | 363 (26.6%) | 123 (28.8%) | 537 (25.9%) | 537 (25.7%) |
| Total | 7 (100%) | 3 (100%) | 10 (100%) | 285 (100%) | 1364 (100%) | 427 (100%) | 2076 (100%) | 2086 (100%) |
| Person-time exposure (year) | | | | | | | | |
| <3 Months | 0.48 | 0 | 0.48 | 16.00 | 35.98 | 13.52 | 65.50 | 65.98 |
| >=3 Months | 0.71 | 2.12 | 2.83 | 120.21 | 1026.20 | 293.66 | 1440.07 | 1442.90 |
| >=6 Months | 0 | 1.69 | 1.69 | 104.91 | 896.70 | 266.81 | 1268.42 | 1270.11 |
| >=12 months | 0 | 0 | 0 | 77.42 | 678.17 | 196.93 | 952.51 | 952.51 |
| Total | 1.19 | 2.12 | 3.31 | 136.21 | 1062.17 | 307.19 | 1505.57 | 1508.88 |

**Table SIII.2** presents the extent of exposure to serplulimab by age group and gender in the pivotal studies of HLX10-005-SCLC301, HLX10-002-NSCLC301, HLX10-007-EC301 and HLX10-004-NSCLC303, and in the Pooled Safety Set, respectively. Overall, more patients below the age of 65 years were treated with serplulimab (N=1 312) compared to patients older than 65 years (N=774). Overall, more male patients (N=1 661) have been treated with serplulimab compared to female patients (N=425).

**Table SIII.2.1：Age group and gender in Pivotal Studies**

| | HLX10-005-SCLC301 (N=389) | HLX10-002-NSCLC301 (N=503) | HLX10-007-EC301 (N=382) | HLX10-004-NSCLC303 (N=455) | Total Population (N=2086) |
|---|---|---|---|---|---|
| Treatment Duration | | | | | |
| Male: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 1038 (49.8%) |
| Female: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 274 (13.1%) |
| Subjects: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 1312 (62.9%) |
| Male: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 623 (29.9%) |
| Female: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 151 (7.2%) |
| Subjects: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 774 (37.1%) |
| Male | [redacted] | [redacted] | [redacted] | [redacted] | 1661 (79.6%) |
| Female | [redacted] | [redacted] | [redacted] | [redacted] | 425 (20.4%) |
| Total | 389 (100%) | 503 (100%) | 382 (100%) | 455 (100%) | 2086 (100%) |
| Person-time exposure (year) | | | | | |
| Male: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 762.09 |
| Female: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 190.31 |
| Subjects: 18-64 | [redacted] | [redacted] | [redacted] | [redacted] | 952.39 |
| Male: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 444.36 |
| Female: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 112.12 |
| Subjects: >=65 | [redacted] | [redacted] | [redacted] | [redacted] | 556.48 |
| Male | [redacted] | [redacted] | [redacted] | [redacted] | 1206.45 |
| Female | [redacted] | [redacted] | [redacted] | [redacted] | 302.43 |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | 1508.88 |

**Table SIII.2.2: Age group and gender in Pooled Safety Set**

| | <RP2D/3D | | | ≥RP2D/3D | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monotherapy (N=7) | Other Combination (N=3) | Total (N=10) | Monotherapy (N=285) | Chemotherapy Combination (N=1364) | Other Combination (N=427) | Total (N=2076) | Total Population (N=2086) |
| Treatment Duration | | | | | | | | |
| Male: 18-64 | 4 (57.1%) | 1 (33.3%) | 5 (50.0%) | 144 (50.5%) | 655 (48.0%) | 234 (54.8%) | 1033 (49.8%) | 1038 (49.8%) |
| Female: 18-64 | 3 (42.9%) | 2 (66.7%) | 5 (50.0%) | 66 (23.2%) | 139 (10.2%) | 64 (15.0%) | 269 (13.0%) | 274 (13.1%) |
| Subjects: 18-64 | 7(100%) | 3(100%) | 10(100%) | 210 (73.7%) | 794 (58.2%) | 298 (69.8%) | 1302 (62.7%) | 1312 (62.9%) |
| Male: >=65 | 0 | 0 | 0 | 61 (21.4%) | 468 (34.3%) | 94 (22.0%) | 623 (30.0%) | 623 (29.9%) |
| Female: >=65 | 0 | 0 | 0 | 14 (4.9%) | 102 (7.5%) | 35 (8.2%) | 151 (7.3%) | 151 (7.2%) |
| Subjects: >=65 | 0 | 0 | 0 | 75 (26.3%) | 570 (41.8%) | 129 (30.2%) | 774 (37.3%) | 774 (37.1%) |
| Male | 4 (57.1%) | 1 (33.3%) | 5 (50.0%) | 205 (71.9%) | 1123 (82.3%) | 328 (76.8%) | 1656 (79.8%) | 1661 (79.6%) |
| Female | 3 (42.9%) | 2 (66.7%) | 5 (50.0%) | 80 (28.1%) | 241 (17.7%) | 99 (23.2%) | 420 (20.2%) | 425 (20.4%) |
| Total | 7 (100%) | 3 (100%) | 10 (100%) | 285 (100%) | 1364 (100%) | 427 (100%) | 2076 (100%) | 2086 (100%) |
| Person-time exposure (year) | | | | | | | | |
| Male: 18-64 | 0.96 | 0.42 | 1.38 | 71.20 | 514.69 | 174.83 | 760.71 | 762.09 |
| Female: 18-64 | 0.24 | 1.69 | 1.93 | 33.67 | 115.66 | 39.05 | 188.38 | 190.31 |
| Subjects: 18-64 | 1.19 | 2.12 | 3.31 | 104.86 | 630.34 | 213.88 | 949.08 | 952.39 |
| Male: >=65 | 0 | 0 | 0 | 26.78 | 346.81 | 70.77 | 444.36 | 444.36 |
| Female: >=65 | 0 | 0 | 0 | 4.56 | 85.02 | 22.54 | 112.12 | 112.12 |
| Subjects: >=65 | 0 | 0 | 0 | 31.34 | 431.83 | 93.31 | 556.48 | 556.48 |
| Male | 0.96 | 0.42 | 1.38 | 97.97 | 861.50 | 245.60 | 1205.07 | 1206.45 |
| Female | 0.24 | 1.69 | 1.93 | 38.23 | 200.67 | 61.59 | 300.50 | 302.43 |
| Total | 1.19 | 2.12 | 3.31 | 136.21 | 1062.17 | 307.19 | 1505.57 | 1508.88 |

**Table SIII.3** presents exposure to serplulimab by dose in the pivotal studies of HLX10-005-SCLC301, HLX10-002-NSCLC301, HLX10-007-EC301, and HLX10-004-NSCLC303, and in the Pooled Safety Set, respectively.

**Table SIII.3.1: Extent of Exposure by Dose in Pivotal Studies**

| | HLX10-005-SCLC301 (N=389) | HLX10-002-NSCLC301 (N=503) | HLX10-007-EC301 (N=382) | HLX10-004-NSCLC303 (N=455) | Total Population (N=2086) |
|---|---|---|---|---|---|
| Person-time exposure (year) | [redacted] | [redacted] | [redacted] | [redacted] | 1508.88 |

**Table SIII.3.2: Extent of Exposure by Dose in Pooled Safety Set**

| | <RP2D/3D | | | ≥RP2D/3D | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monotherapy (N=7) | Other Combination (N=3) | Total (N=10) | Monotherapy (N=285) | Chemotherapy Combination (N=1364) | Other Combination (N=427) | Total (N=2076) | Total Population (N=2086) |
| Person-time exposure (year) | 1.19 | 2.12 | 3.31 | 136.21 | 1062.17 | 307.19 | 1505.57 | 1508.88 |

**Table SIII.4** summarises the extent of exposure to serplulimab by racial origin in the pivotal studies of HLX10-005-SCLC301, HLX10-002-NSCLC301, HLX10-007-EC301 and HLX10-004-NSCLC303, and in the Pooled Safety Set, respectively. The majority of patients treated with serplulimab have been Asian (N=1 818), followed by White (N=268).

**Table SIII.4.1: Ethnic Origin in Pivotal Studies**

| | HLX10-005-SCLC301 (N=389) | HLX10-002-NSCLC301 (N=503) | HLX10-007-EC301 (N=382) | HLX10-004-NSCLC303 (N=455) | Total Population (N=2086) |
|---|---|---|---|---|---|
| Treatment Duration | | | | | |
| Asian | [redacted] | [redacted] | [redacted] | [redacted] | 1818 (87.2%) |
| White | [redacted] | [redacted] | [redacted] | [redacted] | 268 (12.8%) |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | 2086 (100%) |
| Person-time exposure (year) | | | | | |
| Asian | [redacted] | [redacted] | [redacted] | [redacted] | 1289.36 |
| White | [redacted] | [redacted] | [redacted] | [redacted] | 219.52 |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | 1508.88 |

**Table SIII.4.2: Ethnic Origin in Pooled Safety Set**

| | <RP2D/3D | | | ≥RP2D/3D | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monotherapy (N=7) | Other Combination (N=3) | Total (N=10) | Monotherapy (N=285) | Chemotherapy Combination (N=1364) | Other Combination (N=427) | Total (N=2076) | Total Population (N=2086) |
| Treatment Duration | | | | | | | | |
| Asian | 7 (100%) | 3 (100%) | 10 (100%) | 262 (91.9%) | 1119 (82.0%) | 427 (100%) | 1808 (87.1%) | 1818 (87.2%) |
| White | 0 | 0 | 0 | 23 (8.1%) | 245 (18.0%) | 0 | 268 (12.9%) | 268 (12.8%) |
| Total | 7 (100%) | 3 (100%) | 10 (100%) | 285 (100%) | 1364 (100%) | 427 (100%) | 2076 (100%) | 2086 (100%) |
| Person-time exposure (year) | | | | | | | | |
| Asian | 1.19 | 2.12 | 3.31 | 123.58 | 855.28 | 307.19 | 1286.05 | 1289.36 |
| White | 0 | 0 | 0 | 12.63 | 206.89 | 0 | 219.52 | 219.52 |
| Total | 1.19 | 2.12 | 3.31 | 136.21 | 1062.17 | 307.19 | 1505.57 | 1508.88 |

# Part II: Module SIV - Populations not studied in clinical trials

## SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

**Criterion 1: Other active malignancies within 5 years or at the same time. Localised tumours that have been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder carcinoma, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ are acceptable.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with a history of other active malignancies within 5 years or at the same time have not been established. The efficacy and safety of serplulimab in other cancer indications is currently being investigated.

**Criterion 2: Patients who are preparing for or have received an organ or bone marrow transplant.**

Reason for exclusion:

Patients were excluded based on the theoretical concern of graft rejection.

Is it considered to be included as missing information?: No

Rationale:

No patients treated with organ or bone marrow transplant have been included in the clinical trials with serplulimab. It will be monitored in post-marketing activities.

**Criterion 3: Patients with pleural or pericardial effusions or ascites requiring clinical intervention.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in these patients have not been established. Use of serplulimab in this population is not expected to be substantial.

**Criterion 4: Patients with known or documented active central nervous system (CNS) metastases and/or carcinomatous meningitis at screening. However, the following subjects are allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (i.e., no progressive central nervous system symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤ 1.5 cm) may be included, but are required to receive regular brain imaging as a site of lesion. 2) Subjects with treated brain metastases which have been stable for at least 1 month, with no evidence of new or enlarging brain metastases, and**

**with steroids discontinued 3 days prior to study drug administration. Stable brain metastases here should be confirmed before the first dose of the study drugs.**

Reason for exclusion:

The activity of serplulimab in active CNS metastases and/or carcinomatous meningitis has not been established.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with active CNS metastases have not been established. The Summary of Product Characteristics (SmPC) highlights that the population with active brain metastases was excluded from the clinical trial.

**Criterion 5: Patients with myocardial infarction and poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for males and ≥ 470 ms for females) (QTc intervals are calculated by Fridericia's formula) within half a year prior to the first dose of the study drugs.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with clinically significant cardiovascular disease have not been established. The SmPC highlights that the population who has history of significant cardiovascular disease (e.g. myocardial infarction within half a year) was excluded from the clinical trial.

**Criterion 6: Class III to IV cardiac insufficiency according to the New York Heart Association (NYHA) classification or an left ventricular ejection fraction (LVEF) < 50% by cardiac color Doppler.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with clinically significant cardiovascular disease have not been established. The SmPC highlights that the population who has history of significant cardiovascular disease was excluded from the clinical trial.

**Criterion 7: Subject with peripheral neuropathy ≥ Grade 2 by Common terminology criteria for adverse events (CTCAE).**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with peripheral neuropathy ≥ Grade 2 by CTCAE have not been established. The risks of serplulimab in this population are not expected to differ from other patients without peripheral neuropathy.

**Criterion 8: With human immunodeficiency virus (HIV) infection.**

Reason for exclusion:

The impact of immune checkpoint inhibitors (ICIs) on HIV remains unknown. Patients were excluded based on the fact that chronic infections are known to induce T-cell exhaustion and the theoretical concern that serplulimab could cause an inflammatory reaction against those pathogens by reinvigorating the antipathogen immune response.

Is it considered to be included as missing information?: Yes

**Criterion 9: With active pulmonary tuberculosis.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with active pulmonary tuberculosis have not been established. The SmPC highlights that the population with active tuberculosis was excluded from the clinical trial.

**Criterion 10: Subjects with previous and current interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity as judged by the investigator.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in these patients have not been established. The SmPC highlights that the population who had history of pneumonitis or interstitial lung disease was excluded from the clinical trial.

**Criterion 11: With Hepatitis B (positive test for HBsAg or HBcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). With Hepatitis B and C co-infection (positive test for HBsAg or HBcAb and positive test for HCV antibody).**

Reason for exclusion:

The impact of ICIs on Hepatitis B or Hepatitis C remains unknown. Patients were excluded based on the fact that chronic infections are known to induce T-cell exhaustion and the theoretical concern that serplulimab could cause an inflammatory reaction against those pathogens by reinvigorating the antipathogen immune response.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in these patients have not been established. The SmPC highlights that the population with hepatitis B or C infection was excluded from the clinical trial.

**Criterion 12: Patients with known active or suspected autoimmune diseases. Subjects in stable state and requiring no systemic treatment with immunosuppressive agents are included.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: Yes

**Criterion 13: Have received treatment with live vaccines within 28 days prior to the first administration of study drugs.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

In clinical practice it is expected that some patients will receive non-oncology vaccine therapies for prevention of infectious disease and it is possible that patients treated with serplulimab may be at an increased risk for immune-mediated adverse reactions after receiving the vaccine. The SmPC highlights the population receiving live attenuated vaccine within 28 days prior to serplulimab administration was excluded from the clinical trial. There are warnings and guidance in the serplulimab SmPC concerning the risk of immune-mediated adverse reactions and the treatment to be administered based on the severity of reactions should they occur.

**Criterion 14: Subjects requiring treatment with systemic corticosteroids (>10 mg/day prednisone efficacy dosage) or other immunosuppressive drugs within 14 days prior to the first administration of the study drugs or during the study. However, subjects are allowed to be enrolled under the following conditions: in the absence of active autoimmune disease, subjects are allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at dosages equivalent to ≤ 10 mg/day of prednisone efficacy.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

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 SmPC highlights that the

population with systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab was excluded from the clinical trial. The use of systemic corticosteroids or immunosuppressants before starting serplulimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy per section 4.5 of serplulimab SmPC.

**Criterion 15: With any active infection requiring systemic anti-infective therapy within 14 days prior to the first administration of the study drugs.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in these patients have not been established. The SmPC highlights that this population with any active infection requiring systemic anti-infective therapy within 14 days prior to the first dose was excluded from the clinical trial.

**Criterion 16: Have received major surgery within 28 days prior to the first dose of the study drugs, major surgery is defined as: any surgeries requiring at least 3 weeks of postoperative recovery time before receiving the study treatment. Patients with a history of tumour needle biopsy or lymph node incisional biopsy are included.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

Patients who recently have undergone major surgery may benefit from serplulimab therapy.

**Criterion 17: Having received radical radiation therapy within 3 months prior to study medications. Note: Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions is allowed according to local standards and completed 14 days prior to the first dose. Radiotherapy covering more than 30% of the bone marrow area within 28 days prior to the first dose is not allowed.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

In clinical practice patients treated with serplulimab may also be treated with concurrent anticancer therapy.

**Criterion 18: The subject has previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, CTLA4, etc. The Subject may receive other anti-tumour therapies during the study, such as chemotherapy, targeted**

**therapy, or radiotherapy (except palliative radiotherapy). Or be in any other ongoing clinical study, or the end of the previous clinical study treatment is less than 14 days from the planned start of this study.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

In clinical practice patients treated with serplulimab may have previously received checkpoint inhibitors either in clinical trials or in clinical practice. Patients administered ICIs may experience immune-mediated adverse reactions. There are extensive warnings and guidance in the serplulimab SmPC concerning the risk of immune-mediated adverse reactions and the treatment to be administered based on the severity of reactions should they occur. Other immunosuppressants before starting serplulimab should be avoided because their potential interference with the pharmacodynamic activity and efficacy per section 4.5 of serplulimab SmPC.

**Criterion 19: Known history of severe allergy to any monoclonal antibody and chemotherapy drugs.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

Severe infusion reaction is an important identified risk of serplulimab. Patients who have known history of hypersensitive should not receive serplulimab in clinical practice. As serplulimab treatment is initiated and supervised by physician experienced in the treatment of cancer, it should be treated available if hypersensitivity occur in clinical practice. The SmPC highlights that this population with a history of hypersensitivity to another monoclonal antibody was excluded from the clinical trial.

**Criterion 20: Known history of psychotropics abuse or drug abuse or alcoholism.**

Reason for exclusion:

Avoid the factors that may confound understanding of the efficacy and safety profile of serplulimab in the clinical trial.

Is it considered to be included as missing information?: No

Rationale:

The safety and efficacy of serplulimab in patients with known history of psychotropics abuse or drug abuse or alcoholism have not been established. Use of serplulimab in this population is not expected to be substantial.

**Criterion 21: Pregnant or lactating women.**

Reason for exclusion:

Avoid potential harm to the unborn foetus and breastfed infants.

Is it considered to be included as missing information?: No

Rationale:

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. 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.

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.

## SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programmes are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

Safety data are available for 2 086 patients in the clinical programmes treated with serplulimab. Among those patients, 611 patients were treated < 3 months, and 1 475 patients were treated for ≥ 3 months in which 994 patients ≥ 6 months, 537 patients ≥ 12 months in the clinical programmes.

The sample size allows the detection of very common, common and uncommon adverse reactions, but does not allow the detection of very rare adverse reactions. Those reactions will be closely monitored in post-marketing activities.

## SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

**Table SIV.3: Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programmes. |
| Breastfeeding women | |
| Patients with relevant comorbidities:<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• Patients with a disease severity different from inclusion criteria in clinical trials | **Patients with hepatic impairment:**<br>For participation in pivotal studies, subjects were required to have an adequate hepatic function.<br>Total bilirubin (TBIL): ≤ 1.5×upper limit of normal (ULN);<br>Alanine transaminase (ALT): ≤ 2.5×ULN; ≤ 5×ULN for patients with liver metastases; |

| | |
|---|---|
| | Aspartic transaminase (AST): ≤ 2.5×ULN; ≤ 5×ULN for patients with liver metastases.<br><br>**<u>Patients with renal impairment:</u>**<br><br>For participation in the pivotal studies, subjects were required to have an adequate renal function.<br><br>Creatinine (Cr) ≤ 1.5×ULN; In case of > 1.5×ULN, creatinine clearance ≥ 50 mL/min according to Cockcroft-Gault formula.<br><br>**<u>Patients with cardiovascular impairment:</u>**<br><br>Patients with clinically significant cardiovascular disease were excluded from clinical trial participation: myocardial infarction within half a year before the first dose of the study drug; poorly controlled arrhythmia (including QTc intervals ≥ 450 ms for males and ≥ 470 ms for females) (QTc intervals are calculated by Fridericia's formula); Class III to IV cardiac insufficiency according to NYHA classification or an LVEF < 50% by cardiac color Doppler.<br><br>**<u>Immunocompromised patients:</u>**<br><br>The safety and efficacy of serplulimab in immunocompromised patients is limited in the clinical trials. The post-marketing activities may provide further information concerning the efficacy and safety of serplulimab in this population.<br><br>**<u>Patients with a disease severity different from inclusion criteria in clinical trials:</u>**<br><br>Serplulimab is being studied in subjects with advanced metastatic disease. The safety population has a heavy burden of disease with extensive visceral organ involvement. |
| Population with relevant different ethnic origin | Serplulimab is being studied in subjects with cancer worldwide from all racial origins. No major differences were observed when adverse events were analysed by the subjects' racial origin. There are currently no data indicating that specific ethnic backgrounds may impact the clinical safety of serplulimab. |
| Subpopulations carrying relevant genetic polymorphisms | No information is available regarding the effects of serplulimab in sub-populations carrying known and relevant genetic polymorphisms. |
| Other | The populations excluded from clinical trial participation are presented in Section SIV.1. Some patients with certain conditions were excluded from clinical trial including patients with active CNS metastases and/or carcinomatous meningitis; a history of other malignancies within the last 5 years; organ transplant; active infection with HIV, or hepatitis B or C, etc. |

# Part II: Module SV - Post-authorisation experience

## SV.1. Post-authorisation exposure

### SV.1.1. Method used to calculate exposure

The methodology used to calculate the exposure is based on serplulimab dose required for treatment. Based on median progression-free survival (PFS) data from pivotal studies, estimated patient composition and anticipated lower compliance in the real real-world, [redacted] treatment cycles were used for analysis. It is assumed that a patient averagely receives [redacted] mg serplulimab for [redacted] cycles of treatment. Hence, the patient will consume a total of [redacted] mg of serplulimab during the treatment cycles.

No. of patient exposure = (mg of drug sold)/ (mg of drug required for treatment cycles [[redacted] mg])

### SV.1.2. Exposure

Cumulatively, [redacted] vials (100 mg/vial) were sold. Based on the above methodology, [redacted] patients were exposed to serplulimab by 21Mar2025.

The estimated patient exposure for serplulimab is presented in **Table SV.1.2**.

**Table SV.1.2: Cumulative Patient Exposure from Marketing Experience (Presented in patient number)**

| Country | Cumulative Exposure |
|---|---|
| China | [redacted] |
| Indonesia | [redacted] |
| **Total** | [redacted] |

# Part II: Module SVI - Additional EU requirements for the safety specification

## Potential for misuse for illegal purposes

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of haemoglobin levels. The lack of evidence of such side-effects that may lead to misuse for illegal purposes, in addition to the legal status of serplulimab is prescription only, which means serplulimab should be administered under the close supervision of a physician, make it highly unlikely that there is a potential for misuse of serplulimab for illegal purposes. To date, no reports of misuse or serplulimab for illegal purposes have been received.

# Part II: Module SVII - Identified and potential risks

Important identified risks for serplulimab include immune-mediated adverse reactions and severe infusion reactions.

There were no important potential risks for serplulimab.

## SVII.1. Identification of safety concerns in the initial RMP submission

Immune-mediated adverse reactions are not unexpected as serplulimab binds to PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2, which can potentiate T-cell responses and lead to immune-mediated effects. Immune-mediated adverse reactions were observed in patients treated with serplulimab in the clinical trials and confirmed as important identified risk.

Severe infusion reactions, including hypersensitivity and anaphylactic reaction, occurred in patients receiving serplulimab in the clinical trials, was confirmed as important identified risk.

No important potential risks for serplulimab.

### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) included:

*Vomiting, Pyrexia, Asthenia, Decreased appetite, Abdominal distension, Abdominal pain, Mouth ulceration, Nausea, Hypokalaemia and Hyponatraemia.*

The above general adverse reactions had occurred in serplulimab clinical trials, but not considered as important risks of serplulimab considering that serplulimab is used to treat a life-threatening condition.

Adverse reactions with clinical consequences, event seriousness, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation measures in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

*Platelet count decreased, White blood cell count decreased, Neutrophil count decreased, Anaemia, Thrombocytopenia, Neutropenia, Leukopenia and Febrile neutropenia.*

The above haematologic toxicities related adverse reactions commonly occurred in serplulimab clinical trials are well known to prescribers and require no further characterisation and will be monitored via routine pharmacovigilance activities and controlled via routine risk minimisation measures.

Known risks that do not impact the risk-benefit profile:

*Off-label use*

Off-label use is possible with any marketed products, including oncology products which may be used in different cancers other than the approved indication.

Serplulimab is currently being investigated in a variety of other oncology indications including gastric cancer, hepatocellular carcinoma, unresectable/metastatic microsatellite instability-high or mismatch repair deficiency solid tumours, advanced cervical cancer, advanced head and neck tumours, metastatic colorectal cancer.

However, it is possible that as more data become publicly available on the initiated clinical trials in other indications, physicians may use serplulimab in patients with other histologic types of cancers.

The SmPC of serplulimab clearly describes for which indication is authorised. Off-label use is not considered as an important risk of serplulimab.

Other reasons for considering the risks not important:

*Potential for Transmission of Infectious Agents*

The raw materials used for manufacture of serplulimab are not considered to be a significant risk for introducing viral contaminants or transmitting other infectious agents. As all materials used, and/or in contact with serplulimab drug substance and drug product during the manufacturing process, are either animal free or in compliance with EMA/410/01.

The cell banks have been extensively tested for the absence of adventitious agents (bacteria, fungi, mycoplasma and viruses) and were shown to be free of adventitious agents.

In the production process, robust purification steps are designed and validated to provide sufficient viral clearance capacity by chemical inactivation and physical removal according to international council for harmonisation of technical requirements for pharmaceuticals for human use (ICH) Q5A. In addition, in-process tests have been implemented to ensure the absence of potential viral adventitious agents during the cell culture process of serplulimab.

Based on the virus clearance validation and risk assessment performed, the risk for potential contamination with adventitious agents through the manufacturing process of serplulimab is considered to be low.

Potential for Transmission of Infectious Agents was not considered as an important risk of serplulimab.

*Potential for misuse for illegal purposes*

The potential of serplulimab for misuse for illegal purposes is considered as low per the mode of action. The potential for misuse for illegal purposes was not considered as an important risk of serplulimab.

*Medication errors*

As of the data cut-off of this RMP, no significant reports of medication errors have been collected from serplulimab clinical trials.

The SmPC provides clear dosing and administration instructions for serplulimab. Serplulimab is to be prescribed and supervised by a physician experienced in the treatment of cancer, which decreases the risk of medication errors with regard to posology and route of administration.

Medication errors are not considered an important risk of serplulimab.

### SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

**Important Identified Risk 1:** Immune-mediated adverse reactions

Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; immune-mediated uveitis; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in the clinical trials.

0.7% (14/2086) of patients developed immune-mediated myocarditis, of these patients there were 8 (0.4%) patients with Grade 3 and above immune-mediated myocarditis, including 4 (0.2%) patients with fatal outcomes; 1.0% (21/2086) of patients developed immune-mediated pancreatitis, of these patients there were 10 (0.5%) patients with Grade 3 and above immune-mediated pancreatitis, including 1 (<0.1%) patient with a fatal outcome; 4.9% (103/2086) of patients developed immune-mediated lung disease, of these patients there were 36 (1.7%) patients with Grade 3 and above immune-mediated lung disease, including 7 (0.3%) patients with fatal outcomes; 2.0% (41/2086) of patients developed immune-mediated colitis, of these patients there were 14 (0.7%) patients with Grade 3 and above immune-mediated colitis, including 1 (<0.1%) patient with a fatal outcome; 0.8% (16/2086) of patients developed immune-mediated hepatitis, of these patients there were 12 (0.6%) patients with Grade 3 and above immune-mediated hepatitis, including 2 (<0.1%) patients with fatal outcomes. Additionally, 3.7% (77/2086) of patients developed abnormal liver function, of these patients there was no patient with a fatal outcome, 19 (0.9%) patients with Grade 3 and above abnormal liver function; 3.0% (62/2086) of patients developed immune-mediated nephritis and renal dysfunction, of these patients there was no patient with a fatal outcome, 7 (0.3%) patients with Grade 3 and above immune-mediated nephritis and renal dysfunction; 0.9% (19/2086) of patients developed diabetes mellitus/hyperglycaemia, of these patients there was no patient with a fatal outcome, 10 (0.5%) patients with Grade 3 and above diabetes mellitus/hyperglycaemia; 0.7% (15/2086) of patients developed thyroiditis, of these patients there was no patient with a fatal outcome or with Grade 3 and above thyroiditis; 6.7% (139/2086) of patients developed hyperthyroidism, of these patients there was no patient with a fatal outcome or with Grade 3 and above hyperthyroidism; 11.7% (244/2086) of patients developed hypothyroidism, of these patients there was no patient with a fatal outcome, 4 (0.2%) patients with Grade 3 and above hypothyroidism; 0.8% (16/2086) of patients developed pituitary disorders, of these patients there was no patient with a fatal outcome, 2 (<0.1%) patients with Grade 3 and above pituitary disorders; 0.5% (11/2086) of patients developed adrenal gland disorders, of these patients there was no patient with a fatal outcome, 2 (<0.1%) patients with Grade 3 and above adrenal gland disorders; 7.8% (162/2086) of patients developed immune-mediated skin adverse reactions, of these patients there were 19 (0.9%) patients with Grade 3 and above immune-mediated skin adverse reactions, including 1 (<0.1%) patient

with a fatal outcome; <0.1% (1/2086) of patient developed immune-mediated uveitis which was Grade 1; 13.0% (272/2086) of patients developed other immune-mediated adverse reactions, of these patients there were 74 (3.5%) patients with Grade 3 and above other immune-mediated adverse reactions, including 11 (0.5%) patients with fatal outcomes.

Risk-benefit impact:

Immune-mediated adverse reactions may be life-threatening or fatal in individual patients. However immune-mediated adverse reactions are not unexpected effects of immune check point inhibitors, and clinical trials and scientific literature showed that the incidence of immune-mediated adverse reactions is not high. The benefit of serplulimab for treating a life-threatening condition is considered to outweigh the risk of immune-mediated adverse reactions that can be managed in clinical practice through monitoring to prevent serious complications.

The important identified risk will be further monitored and characterised in patients exposed to serplulimab in the ongoing clinical trials and post-marketing activities.

**Important Identified Risk 2:** Severe infusion reactions

Severe infusion reactions were observed in patients treated with serplulimab in the clinical trials. 1.7% (35/2086) of patients developed infusion reactions, of these patients there was no patient with a fatal outcome, 5 (0.2%) patients with Grade 3 and above severe infusion reactions.

Risk-benefit impact:

Infusion-related reactions can be potentially severe. However severe infusion reactions are not unexpected effect of a monoclonal antibody. Overall the benefit of serplulimab for treating a life-threatening condition is considered to outweigh the risk that can be managed in clinical practice.

The important identified risk will be further monitored and characterised in patients exposed to serplulimab in the ongoing clinical trials and post-marketing activities.

**Important Potential Risk:** No important potential risk for serplulimab.

**Missing information:** Long-term safety in immunocompromised patients

Risk-benefit impact: Not included in the clinical development programmes. The post-marketing activities may provide further information concerning the safety of serplulimab in this population.

## SVII.2. New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns or reclassification of safety concerns with the submission of the updated RMP.

## SVII.3. Details of important identified risks, important potential risks, and missing information

Safety data from patients with ES-SCLC who were treated with serplulimab 4.5 mg/kg every three weeks in combination with chemotherapy (carboplatin-etoposide) in the

pivotal study HLX10-005-SCLC301 was included to characterise the safety profile of serplulimab. The safety data included the ES-SCLC population (N=389).

Safety data from patients with non-squamous NSCLC who were treated with serplulimab 4.5 mg/kg every three weeks in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in the pivotal study HLX10-002-NSCLC301 was included to characterise the safety profile of serplulimab. The safety data included the non-squamous NSCLC population (N=503).

Safety data from patients with OSCC who were treated with serplulimab 3.0 mg/kg every two weeks in combination with cisplatin and 5-FU in the pivotal study HLX10-007-EC301 was included to characterise the safety profile of serplulimab. The safety data included the OSCC population (N=382).

Safety data from patients with squamous NSCLC who were treated with serplulimab 4.5 mg/kg every three weeks, monotherapy or in combination with carboplatin and nab-paclitaxel in the pivotal study HLX10-004-NSCLC303 was included to characterise the safety profile of serplulimab. The safety data included the squamous NSCLC population (N=455).

The pooled safety data set included the safety data in the pivotal studies: HLX10-005-SCLC301 (patient: 389) for ES-SCLC, HLX10-002-NSCLC301 (patient: 503) for non-squamous NSCLC, HLX10-007-EC301 (patient: 382) for OSCC, HLX10-004-NSCLC303 (patient: 455) for squamous NSCLC; in the clinical trials with serplulimab single agent: HLX10-010-MSI201 (patient: 108), HLX10-001 (patient: 66), HLX10-008-HCC201 (patient: 21); in the clinical trials with combined chemotherapy: HLX10-011-CC201 (patient: 21); and in the clinical trials with combined other monoclonal antibodies: HLX10HLX04-001 (patient: 26), HLX10-008-HCC201 (patient: 102), HLX10HLX07-001 (patient: 13) was evaluated.

Toxicity of adverse events was graded per National Cancer Institute (NCI) CTCAE version 4.03 for studies HLX10-001, HLX10HLX04-001 and HLX10-007-EC301, CTCAE version 5.0 for other studies.

### SVII.3.1. Presentation of important identified risks and important potential risks

### Important Identified Risks

| **Important Identified Risk:** Immune-mediated adverse reactions | |
|---|---|
| Potential mechanisms: | Serplulimab is a monoclonal antibody that binds to PD-1 receptor, and blocks its interaction with ligands PD-L1 and PD-L2, which can potentiate T-cell responses and lead to immune-mediated effects. Increasing T-cell activity against antigens that are present in tumours and healthy tissue, increasing levels of preexisting autoantibodies and increase in the level of inflammatory cytokines, are possible mechanisms of underlying immune-related adverse event (irAE) (Postow 2018).<br><br>PD-1 is a transmembrane protein expressed by T cells, B cells, immature Langerhans cells, and natural killer (NK) T cells. PD-1 engages with its ligand PD-L1 causing inhibition of T cell responses in peripheral tissues. PD-1 negatively regulate T cell activity to counter autoimmunity by dampening autoreactive T cell proliferation |

| | |
|---|---|
| | either directly or indirectly via regulatory T cells (Tregs). To evade destruction by the host immune response, tumour cells tend to overexpress the ligands of these immune checkpoint receptors, contributing to T cell exhaustion. Blockade of these pathways using monoclonal antibodies targeting PD-1 releases the "brakes" on pre-existing tumour reactive T cells, and thus enhances anti-tumour activity. As anticipated, modulation of immunological parameters and immune functions with ICI results in activation of autoreactive T cells, leading to a unique and distinct spectrum of adverse events called irAEs. Pathologically, irAEs are characterised by lymphocytic and macrophagic infiltration into the non-tumour tissues and subsequent injury (Khunger 2020). |
| Evidence source(s) and strength of evidence: | Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>The safety of serplulimab in combination with carboplatin and etoposide was evaluated in the pivotal study HLX10-005-SCLC301 (389 patients). Immune-mediated adverse reactions (including: immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in this clinical trial.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>The safety of serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 was evaluated in the pivotal study HLX10-002-NSCLC301 (503 patients). Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in this clinical trial.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>The safety of serplulimab in combination with cisplatin and 5-FU was evaluated in the pivotal study HLX10-007-EC301 (382 patients). Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in this clinical trial. |

| | |
|---|---|
| | Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>The safety of serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel was evaluated in the pivotal study HLX10-004-NSCLC303 (455 patients). Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in this clinical trial.<br><br>Serplulimab in pooled safety set<br><br>The safety of serplulimab in the pivotal studies: HLX10-005-SCLC301 (patient: 389) for ES-SCLC, HLX10-002-NSCLC301 (patient: 503) for non-squamous NSCLC, HLX10-007-EC301 (patient: 382) for OSCC, HLX10-004-NSCLC303 (patient: 455) for squamous NSCLC; in the clinical trials with serplulimab single agent: HLX10-010-MSI201 (patient: 108), HLX10-001 (patient: 66), HLX10-008-HCC201 (patient: 21); in the clinical trials with combined chemotherapy: HLX10-011-CC201 (patient: 21); and in the clinical trials with combined other monoclonal antibodies: HLX10HLX04-001 (patient: 26), HLX10-008-HCC201 (patient: 102), HLX10HLX07-001 (patient: 13) was evaluated. Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; immune-mediated uveitis; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in these clinical trials. |
| Characterisation of the risk: | ***Immune-mediated myocarditis***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated myocarditis was not observed in patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Immune-mediated myocarditis was observed in 1.2% (6/503) (95%CI: 0.4%-2.6%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 1.0% (5/503) of patients experienced serious adverse events and 0.2% (1/503) of patients experienced non-serious adverse events. |

| | |
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| | There were 1 (0.2%) patient with a fatal outcome, 1 (0.2%) patient with Grade 4 immune-mediated myocarditis, 1 (0.2%) patient with Grade 3 immune-mediated myocarditis, 2 (0.4%) patients with Grade 2 immune-mediated myocarditis, 1 (0.2%) patient with Grade 1 immune-mediated myocarditis.<br><br>The median time to onset of immune-mediated myocarditis was 2.68 months (range: 0.76 to 7.95 months). The median duration was 0.87 months (range: 0.33 to 5.72 months).<br><br>Serplulimab was discontinued in 0.6% (3/503) of patients and temporarily discontinued in 0.2% (1/503) of patients due to immune-mediated myocarditis. Immune-mediated myocarditis resolved (hereinafter "resolved" includes "resolved", "resolved with sequelae" and "resolving") in 1 (0.2%) patient at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Immune-mediated myocarditis was observed in 0.5% (2/382) (95%CI: 0.1%-1.9%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. There were 2 (0.5%) patients with fatal outcomes.<br><br>The median time to onset of immune-mediated myocarditis was 1.30 months (range: 0.92 to 1.68 months). The median duration was 0.33 months (range: 0.30 to 0.36 months).<br><br>Serplulimab was discontinued in 0.3% (1/382) of patients due to immune-mediated myocarditis. No immune-mediated myocarditis resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Immune-mediated myocarditis was observed in 0.2% (1/455) (95%CI: 0.0%-1.2%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. The patient experienced non-serious adverse event which was Grade 2. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated myocarditis was 6.37 months (range: 6.37 to 6.37 months). The median duration was 4.57 months (range: 4.57 to 4.57 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to immune-mediated myocarditis. No immune-mediated myocarditis resolved in any patients at the time of data cut-off. |

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| | Serplulimab in pooled safety set<br><br>Across clinical studies, 0.7% (14/2086) (95%CI: 0.4%-1.1%) of patients developed immune-mediated myocarditis. In the ≥RP2D/3D dose group (N=2 076), there were 3 patients who received serplulimab monotherapy, 6 patients who received serplulimab in combination with chemotherapy, and 5 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated myocarditis. Among the patients experiencing immune-mediated myocarditis, 0.4% (9/2086) of patients experienced serious adverse events and 0.2% (5/2086) of patients experienced non-serious adverse events. There were 4 (0.2%) patients with fatal outcomes, 1 (<0.1%) patient with Grade 4 immune-mediated myocarditis, 3 (0.1%) patients with Grade 3 immune-mediated myocarditis, 3 (0.1%) patients with Grade 2 immune-mediated myocarditis and 3 (0.1%) patients with Grade 1 immune-mediated myocarditis.<br><br>The median time to onset of immune-mediated myocarditis was 1.71 months (range: 0.26 to 20.70 months). The median duration was 0.79 months (range: 0.30 to 5.72 months).<br><br>Serplulimab was discontinued in 0.3% (6/2086) of patients and temporarily discontinued in 0.2% (4/2086) of patients due to immune-mediated myocarditis. Immune-mediated myocarditis resolved in 3 (0.1%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 24 immune-mediated myocarditis events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated pancreatitis***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated pancreatitis was observed in 0.3% (1/389) (95%CI: 0.0%-1.4%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. The patient experienced serious adverse event which was Grade 4. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated pancreatitis was 1.48 months (range: 1.48 to 1.48 months). The median duration was 0.16 months (range: 0.16 to 0.16 months).<br><br>Serplulimab was discontinued in the patient due to immune-mediated pancreatitis. Immune-mediated pancreatitis resolved in the patient at the time of data cut-off. |

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| | <u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>Immune-mediated pancreatitis was observed in 0.6% (3/503) (95%CI: 0.1%-1.7%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.4% (2/503) of patients experienced serious adverse events and 0.2% (1/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 immune-mediated pancreatitis, 1 (0.2%) patient with Grade 2 immune-mediated pancreatitis, 1 (0.2%) patient with Grade 1 immune-mediated pancreatitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated pancreatitis was 6.87 months (range: 2.86 to 13.67 months).<br><br>Serplulimab was discontinued in 0.4% (2/503) of patients due to immune-mediated pancreatitis. Immune-mediated pancreatitis resolved in 1 (0.2%) patient at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Immune-mediated pancreatitis was observed in 1.3% (5/382) (95%CI: 0.4%-3.0%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.3% (1/382) of patients experienced serious adverse events and 1.0% (4/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 4 immune-mediated pancreatitis, 1 (0.3%) patient with Grade 3 immune-mediated pancreatitis, 2 (0.5%) patients with Grade 2 immune-mediated pancreatitis, and 1 (0.3%) patient with Grade 1 immune-mediated pancreatitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated pancreatitis was 6.18 months (range: 1.91 to 10.18 months). The median duration was 0.77 months (range: 0.56 to 1.35 months).<br><br>Serplulimab was discontinued in 0.3% (1/382) of patients and temporarily discontinued in 0.8% (3/382) of patients due to immune-mediated pancreatitis. Immune-mediated pancreatitis resolved in 3 (0.8%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Immune-mediated pancreatitis was not observed in patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. |

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| | Serplulimab in pooled safety set<br><br>Across clinical studies, 1.0% (21/2086) (95%CI: 0.6%-1.5%) of patients developed immune-mediated pancreatitis. In the <RP2D/3D dose group (N=10), 2 patients who received serplulimab in combination with other monoclonal antibodies experienced immune-mediated pancreatitis. In the ≥RP2D/3D dose group (N=2 076), there were 2 patients who received serplulimab monotherapy, 7 patients who received serplulimab in combination with chemotherapy, and 10 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated pancreatitis. Among the patients experiencing immune-mediated pancreatitis, 0.2% (5/2086) of patients experienced serious adverse events and 0.8% (16/2086) of patients experienced non-serious adverse events. There were 1 (<0.1%) patient with a fatal outcome, 3 (0.1%) patients with Grade 4 immune-mediated pancreatitis, 6 (0.3%) patients with Grade 3 immune-mediated pancreatitis, 4 (0.2%) patients with Grade 2 immune-mediated pancreatitis, 7 (0.3%) patients with Grade 1 immune-mediated pancreatitis.<br><br>The median time to onset of immune-mediated pancreatitis was 2.86 months (range: 0.23 to 13.67 months). The median duration was 0.76 months (range: 0.16 to 10.12 months).<br><br>Serplulimab was discontinued in 0.2% (5/2086) of patients and temporarily discontinued in 0.3% (7/2086) of patients due to immune-mediated pancreatitis. Immune-mediated pancreatitis resolved in 9 (0.4%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 4 immune-mediated pancreatitis events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated lung disease***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated lung disease was observed in 3.1% (12/389) (95%CI: 1.6%-5.3%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 1.5% (6/389) of patients experienced serious adverse events and 1.5% (6/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with a fatal outcome, 3 (0.8%) patients with Grade 3 immune-mediated lung disease, 5 (1.3%) patients with Grade 2 immune-mediated lung disease, 3 (0.8%) patients with Grade 1 immune-mediated lung disease. |

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| | The median time to onset of immune-mediated lung disease was 9.07 months (range: 0.79 to 34.53 months). The median duration was 1.81 months (range: 0.30 to 13.34 months).<br><br>Serplulimab was discontinued in 0.5% (2/389) of patients and temporarily discontinued in 1.5% (6/389) of patients due to immune-mediated lung disease. Immune-mediated lung disease resolved in 6 (1.5%) patients at the time of data cut-off.<br><br><u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>Immune-mediated lung disease was observed in 6.8% (34/503) (95%CI: 4.7%-9.3%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 3.6% (18/503) of patients experienced serious adverse events and 3.2% (16/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with a fatal outcome, 2 (0.4%) patients with Grade 4 immune-mediated lung disease, 7 (1.4%) patients with Grade 3 immune-mediated lung disease, 15 (3.0%) patients with Grade 2 immune-mediated lung disease, 9 (1.8%) patients with Grade 1 immune-mediated lung disease.<br><br>The median time to onset of immune-mediated lung disease was 4.60 months (range: 0.92 to 24.41 months). The median duration was 2.00 months (range: 0.33 to 12.25 months).<br><br>Serplulimab was discontinued in 2.2% (11/503) of patients and temporarily discontinued in 2.8% (14/503) of patients due to immune-mediated lung disease. Immune-mediated lung disease resolved in 5 (1.0%) patients at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Immune-mediated lung disease was observed in 5.0% (19/382) (95%CI: 3.0%-7.7%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 2.6% (10/382) of patients experienced serious adverse events and 2.4% (9/382) of patients experienced non-serious adverse events. There were 3 (0.8%) patients with fatal outcomes, 1 (0.3%) patient with Grade 4 immune-mediated lung disease, 5 (1.3%) patients with Grade 3 immune-mediated lung disease, 7 (1.8%) patients with Grade 2 immune-mediated lung disease, and 3 (0.8%) patients with Grade 1 immune-mediated lung disease.<br><br>The median time to onset of immune-mediated lung disease was 4.11 months (range: 0.95 to 9.92 months). The median duration was 1.59 months (range: 0.10 to 9.07 months).<br><br>Serplulimab was discontinued in 1.0% (4/382) of patients and temporarily discontinued in 2.6% (10/382) of patients due to |

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| | immune-mediated lung disease. Immune-mediated lung disease resolved in 7 (1.8%) patients at the time of data cut-off.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Immune-mediated lung disease was observed in 6.6% (30/455) (95%CI: 4.5%-9.3%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 4.0% (18/455) of patients experienced serious adverse events and 2.6% (12/455) of patients experienced non-serious adverse events. There were 2 (0.4%) patients with fatal outcomes, 1 (0.2%) patient with Grade 4 immune-mediated lung disease, 7 (1.5%) patients with Grade 3 immune-mediated lung disease, 18 (4.0%) patients with Grade 2 immune-mediated lung disease, and 2 (0.4%) patients with Grade 1 immune-mediated lung disease.<br><br>The median time to onset of immune-mediated lung disease was 5.86 months (range: 0.03 to 22.21 months). The median duration was 1.82 months (range: 0.26 to 10.09 months).<br><br>Serplulimab was discontinued in 2.2% (10/455) of patients and temporarily discontinued in 4.6% (21/455) of patients due to immune-mediated lung disease. Immune-mediated lung disease resolved in 17 (3.7%) patients at the time of data cut-off.<br><br>Serplulimab in pooled safety set<br><br>Across clinical studies, 4.9% (103/2086) (95%CI: 4.0%-6.0%) of patients developed immune-mediated lung disease. In the ≥RP2D/3D dose group (N=2 076), there were 11 patients who received serplulimab monotherapy, 74 patients who received serplulimab in combination with chemotherapy, and 18 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated lung disease. Among the patients experiencing immune-mediated lung disease, 2.6% (54/2086) of patients experienced serious adverse events and 2.3% (49/2086) of patients experienced non-serious adverse events. There were 7 (0.3%) patients with fatal outcomes, 4 (0.2%) patients with Grade 4 immune-mediated lung disease, 25 (1.2%) patients with Grade 3 immune-mediated lung disease, 48 (2.3%) patients with Grade 2 immune-mediated lung disease, 19 (0.9%) patients with Grade 1 immune-mediated lung disease.<br><br>The median time to onset of immune-mediated lung disease was 4.40 months (range: 0.03 to 34.53 months). The median duration was 1.76 months (range: 0.10 to 13.34 months).<br><br>Serplulimab was discontinued in 1.3% (28/2086) of patients and temporarily discontinued in 2.6% (54/2086) of patients due to immune-mediated lung disease. Immune-mediated lung disease resolved in 40 (1.9%) patients at the time of data cut-off. |

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| | Post-Marketing Data Sources<br><br>As of 21Mar2025, 66 immune-mediated lung disease events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated colitis***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated colitis was observed in 1.8% (7/389) (95%CI: 0.7%-3.7%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 0.3% (1/389) of patients experienced serious adverse events and 1.5% (6/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 3 immune-mediated colitis, 2 (0.5%) patients with Grade 2 immune-mediated colitis, 4 (1.0%) patients with Grade 1 immune-mediated colitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated colitis was 3.22 months (range: 0.10 to 7.95 months). The median duration was 0.54 months (range: 0.33 to 1.05 months).<br><br>Serplulimab was discontinued in 0.3% (1/389) of patients due to immune-mediated colitis. Immune-mediated colitis resolved in 5 (1.3%) patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Immune-mediated colitis was observed in 1.4% (7/503) (95%CI: 0.6%-2.8%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 1.2% (6/503) of patients experienced serious adverse events and 0.2% (1/503) of patients experienced non-serious adverse events. There were 6 (1.2%) patients with Grade 3 immune-mediated colitis, 1 (0.2%) patient with Grade 2 immune-mediated colitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated colitis was 8.18 months (range: 2.23 to 30.55 months). The median duration was 0.80 months (range: 0.16 to 8.94 months).<br><br>Serplulimab was discontinued in 0.2% (1/503) of patients and temporarily discontinued in 1.2% (6/503) of patients due to immune-mediated colitis. No immune-mediated colitis resolved at the time of data cut-off. |

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| | Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Immune-mediated colitis was observed in 1.3% (5/382) (95%CI: 0.4%-3.0%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. All patients experienced non-serious adverse events. There were 3 (0.8%) patients with Grade 2 immune-mediated colitis, and 2 (0.5%) patients with Grade 1 immune-mediated colitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated colitis was 1.05 months (range: 0.07 to 7.85 months). The median duration was 0.23 months (range: 0.10 to 2.43 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/382) of patients due to immune-mediated colitis. Immune-mediated colitis resolved in 4 (1.0%) patients at the time of data cut-off.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Immune-mediated colitis was observed in 2.0% (9/455) (95%CI: 0.9%-3.7%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.9% (4/455) of patients experienced serious adverse events and 1.1% (5/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with a fatal outcome, 2 (0.4%) patients with Grade 3 immune-mediated colitis, 4 (0.9%) patients with Grade 2 immune-mediated colitis, and 2 (0.4%) patients with Grade 1 immune-mediated colitis.<br><br>The median time to onset of immune-mediated colitis was 3.68 months (range: 0.03 to 17.87 months). The median duration was 0.25 months (range: 0.03 to 4.07 months).<br><br>Serplulimab was discontinued in 0.4% (2/455) of patients and temporarily discontinued in 1.1% (5/455) of patients due to immune-mediated colitis. Immune-mediated colitis resolved in 7 (1.5%) patients at the time of data cut-off.<br><br>Serplulimab in pooled safety set<br><br>Across clinical studies, 2.0% (41/2086) (95%CI: 1.4%-2.7%) of patients developed immune-mediated colitis. In the ≥RP2D/3D dose group (N=2 076), there were 9 patients who received serplulimab monotherapy, 24 patients who received serplulimab in combination with chemotherapy, and 8 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated colitis. Among the patients experiencing immune-mediated colitis, 0.6% (13/2086) of patients experienced serious adverse events and 1.3% (28/2086) of patients experienced non-serious adverse events. There were 1 (<0.1%) patient with a fatal outcome, 13 (0.6%) patients with Grade 3 immune-mediated colitis, |

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| | 14 (0.7%) patients with Grade 2 immune-mediated colitis, 13 (0.6%) patients with Grade 1 immune-mediated colitis.<br><br>The median time to onset of immune-mediated colitis was 3.35 months (range: 0.03 to 30.55 months). The median duration was 0.43 months (range: 0.03 to 8.94 months).<br><br>Serplulimab was discontinued in 0.2% (5/2086) of patients and temporarily discontinued in 0.7% (15/2086) of patients due to immune-mediated colitis. Immune-mediated colitis resolved in 24 (1.2%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 10 immune-mediated colitis events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated hepatitis***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated hepatitis was observed in 0.5% (2/389) (95%CI: 0.1%-1.8%) of patient with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 0.3% (1/389) of patients experienced serious adverse events and 0.3% (1/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 3 and 1 (0.3%) patient with Grade 2 hepatitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated hepatitis was 15.47 months (range: 4.17 to 26.78 months). The median duration was 1.48 months (range: 1.48 to 1.48 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/389) of patients due to immune-mediated hepatitis. Immune-mediated hepatitis resolved in 2 (0.5%) patients at the time of data cut-off.<br><br>Abnormal liver function was observed in 4.4% (17/389) (95%CI: 2.6%-6.9%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 1.0% (4/389) of patients experienced serious adverse events and 3.3% (13/389) of patients experienced non-serious adverse events. There were 4 (1.0%) patients with Grade 3 abnormal liver function, 7 (1.8%) patients with Grade 2 abnormal liver function, 6 (1.5%) patients with Grade 1 abnormal liver function. There was no patient with a fatal outcome.<br><br>The median time to onset of abnormal liver function was 2.10 months (range: 0.69 to 45.31 months). The median duration was 1.64 months (range: 1.15 to 13.40 months). |

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| | Serplulimab was discontinued in 0.3% (1/389) of patients and temporarily discontinued in 2.3% (9/389) of patients due to abnormal liver function. Abnormal liver function resolved in 4 (1.0%) patients at the time of data cut-off.<br><br><u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>Immune-mediated hepatitis was observed in 0.6% (3/503) (95%CI: 0.1%-1.7%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. All patients experienced serious adverse events. There were 1 (0.2%) patient with Grade 4 immune-mediated hepatitis, 2 (0.4%) patients with Grade 3 immune-mediated hepatitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated hepatitis was 1.51 months (range: 0.69 to 1.94 months). The median duration was 3.45 months (range: 0.39 to 6.51 months).<br><br>Serplulimab was discontinued in 0.4% (2/503) of patients and temporarily discontinued in 0.2% (1/503) of patients due to immune-mediated hepatitis. No immune-mediated hepatitis resolved in any patients at the time of data cut-off.<br><br>Abnormal liver function was observed in 1.6% (8/503) (95%CI: 0.7%-3.1%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.4% (2/503) of patients experienced serious adverse events and 1.2% (6/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 4 abnormal liver function, 1 (0.2%) patient with Grade 3 abnormal liver function, 6 (1.2%) patients with Grade 1 abnormal liver function. There was no patient with a fatal outcome.<br><br>The median time to onset of abnormal liver function was 6.05 months (range: 0.72 to 25.92 months). The median duration was 1.68 months (range: 0.59 to 2.10 months).<br><br>Serplulimab was discontinued in 0.2% (1/503) of patients and temporarily discontinued in 0.2% (1/503) of patients due to abnormal liver function. No abnormal liver function resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Immune-mediated hepatitis was observed in 0.3% (1/382) (95%CI: 0.0%-1.4%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. The patient experienced non-serious adverse event which was Grade 2. There was no patient with a fatal outcome. |

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| | The median time to onset of immune-mediated hepatitis was 11.60 months (range: 11.60 to 11.60 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/382) of patients due to immune-mediated hepatitis. No hepatitis resolved in any patients at the time of data cut-off.<br><br>Abnormal liver function was observed in 2.9% (11/382) (95%CI: 1.4%-5.1%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.3% (1/382) of patients experienced serious adverse events and 2.6% (10/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 4 abnormal liver function, 4 (1.0%) patients with Grade 3 abnormal liver function, 1 (0.3%) patient with Grade 2 abnormal liver function, and 5 (1.3%) patients with Grade 1 abnormal liver function. There was no patient with a fatal outcome.<br><br>The median time to onset of abnormal liver function was 4.21 months (range: 0.39 to 6.44 months). The median duration was 0.90 months (range: 0.53 to 5.36 months).<br><br>Serplulimab was temporarily discontinued in 1.6% (6/382) of patients due to abnormal liver function. Abnormal liver function resolved in 6 (1.6%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Immune-mediated hepatitis was observed in 0.7% (3/455) (95%CI: 0.1%-1.9%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.2% (1/455) of patients experienced serious adverse events and 0.4% (2/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 4 immune-mediated hepatitis, 1 (0.2%) patient with Grade 2 immune-mediated hepatitis, and 1 (0.2%) patient with Grade 1 immune-mediated hepatitis. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated hepatitis was 6.24 months (range: 0.72 to 19.25 months). The median duration was 4.29 months (range: 0.10 to 8.48 months).<br><br>Serplulimab was discontinued in 0.2% (1/455) of patients due to immune-mediated hepatitis. Immune-mediated hepatitis resolved in 2 (0.4%) patients at the time data cut-off.<br><br>Abnormal liver function was observed in 2.9% (13/455) (95%CI: 1.5%-4.8%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.2% (1/455) of patients experienced serious adverse events and 2.6% (12/455) of patients experienced non-serious |

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| | adverse events. There were 3 (0.7%) patients with Grade 3 abnormal liver function, 1 (0.2%) patient with Grade 2 abnormal liver function, and 9 (2.0%) patients with Grade 1 abnormal liver function. There was no patient with a fatal outcome.<br><br>The median time to onset of abnormal liver function was 5.39 months (range: 0.66 to 22.28 months). The median duration was 0.72 months (range: 0.46 to 2.83 months).<br><br>Serplulimab was temporarily discontinued in 0.9% (4/455) of patients due to abnormal liver function. Abnormal liver function resolved in 9 (2.0%) patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 0.8% (16/2086) (95%CI: 0.4%-1.2%) of patients developed immune-mediated hepatitis. In the ≥RP2D/3D dose group (N=2 076), there were 7 patients who received serplulimab monotherapy, 7 patients who received serplulimab in combination with chemotherapy, and 2 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated hepatitis. Among the patients experiencing immune-mediated hepatitis, 0.5% (10/2086) of patients experienced serious adverse events and 0.3% (6/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with fatal outcomes, 3 (0.1%) patients with Grade 4 immune-mediated hepatitis, 7 (0.3%) patients with Grade 3 immune-mediated hepatitis, 3 (0.1%) patients with Grade 2 immune-mediated hepatitis, 1 (<0.1%) patient with Grade 1 immune-mediated hepatitis.<br><br>The median time to onset of immune-mediated hepatitis was 2.48 months (range: 0.36 to 26.78 months). The median duration was 0.95 months (range: 0.10 to 8.48 months).<br><br>Serplulimab was discontinued in 0.3% (7/2086) of patients and temporarily discontinued in 0.3% (6/2086) of patients due to immune-mediated hepatitis. Immune-mediated hepatitis resolved in 7 (0.3%) patients at the time of data cut-off.<br><br>Across clinical studies, 3.7% (77/2086) (95%CI: 2.9%-4.6%) of patients developed abnormal liver function. In the <RP2D/3D dose group (N=10), 2 patients who received serplulimab in combination with other monoclonal antibodies experienced abnormal liver function. In the ≥RP2D/3D dose group (N=2 076), there were 7 patients who received serplulimab monotherapy, 46 patients who received serplulimab in combination with chemotherapy, and 22 patients who received serplulimab in combination with other monoclonal antibodies, experienced abnormal liver function. Among the patients experiencing abnormal liver function, 0.5% (10/2086) of patients experienced serious adverse events and 3.2% (67/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with Grade 4 abnormal liver function, 17 (0.8%) |

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| | patients with Grade 3 abnormal liver function, 17 (0.8%) patients with Grade 2 abnormal liver function, 41 (2.0%) patients with Grade 1 abnormal liver function. There was no patient with a fatal outcome.<br><br>The median time to onset of abnormal liver function was 2.30 months (range: 0.07 to 45.31 months). The median duration was 1.31 months (range: 0.26 to 17.54 months).<br><br>Serplulimab was discontinued in 0.2% (5/2086) of patients and temporarily discontinued in 1.1% (23/2086) of patients due to abnormal liver function. Abnormal liver function resolved in 33 (1.6%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 23 immune-mediated hepatitis events and 9 abnormal liver function events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated nephritis and renal dysfunction***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated nephritis and renal dysfunction was observed in 1.3% (5/389) (95%CI: 0.4%-3.0%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. All patients experienced non-serious adverse events. There were 3 (0.8%) patients with Grade 2 immune-mediated nephritis and renal dysfunction, 2 (0.5%) patients with Grade 1 immune-mediated nephritis and renal dysfunction. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated nephritis and renal dysfunction was 9.49 months (range: 0.79 to 13.60 months). The median duration was 0.94 months (range: 0.20 to 1.68 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/389) of patients due to immune-mediated nephritis and renal dysfunction. Immune-mediated nephritis and renal dysfunction resolved in 1 (0.3%) patient at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Immune-mediated nephritis and renal dysfunction was observed in 1.0% (5/503) (95%CI: 0.3%-2.3%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.2% (1/503) of patients experienced serious adverse events and 0.8% (4/503) of patients experienced non-serious adverse events. There were 4 (0.8%) patients with Grade 2 |

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| | immune-mediated nephritis and renal dysfunction, 1 (0.2%) patient with Grade 1 immune-mediated nephritis and renal dysfunction. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated nephritis and renal dysfunction was 4.27 months (range: 2.73 to 11.40 months). The median duration was 3.15 months (range: 1.48 to 4.83 months).<br><br>Serplulimab was discontinued in 0.2% (1/503) of patients and temporarily discontinued in 0.2% (1/503) of patients due to immune-mediated nephritis and renal dysfunction. No immune-mediated nephritis and renal dysfunction resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Immune-mediated nephritis and renal dysfunction was observed in 6.3% (24/382) (95%CI: 4.1%-9.2%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.8% (3/382) of patients experienced serious adverse events and 5.5% (21/382) of patients experienced non-serious adverse events. There were 2 (0.5%) patients with Grade 3 immune-mediated nephritis and renal dysfunction, 4 (1.0%) patients with Grade 2 immune-mediated nephritis and renal dysfunction, and 18 (4.7%) patients with Grade 1 immune-mediated nephritis and renal dysfunction. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated nephritis and renal dysfunction was 2.32 months (range: 0.39 to 14.92 months). The median duration was 1.08 months (range: 0.30 to 6.28 months).<br><br>Serplulimab was discontinued in 0.3% (1/382) of patients and temporarily discontinued in 1.0% (4/382) of patients due to immune-mediated nephritis and renal dysfunction. Immune-mediated nephritis and renal dysfunction resolved in 15 (3.9%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Immune-mediated nephritis and renal dysfunction was observed in 2.4% (11/455) (95%CI: 1.2%-4.3%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 1.1% (5/455) of patients experienced serious adverse events and 1.3% (6/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 4 immune-mediated nephritis and renal dysfunction, 3 (0.7%) patients with Grade 3 immune-mediated nephritis and renal dysfunction, 3 (0.7%) patients with Grade 2 immune-mediated nephritis and renal dysfunction, and 4 (0.9%) patients with Grade 1 |

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| | immune-mediated nephritis and renal dysfunction. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated nephritis and renal dysfunction was 6.54 months (range: 1.41 to 17.77 months). The median duration was 9.33 months (range: 0.72 to 17.94 months).<br><br>Serplulimab was discontinued in 0.7% (3/455) of patients and temporarily discontinued in 0.7% (3/455) of patients due to immune-mediated nephritis and renal dysfunction. Immune-mediated nephritis and renal dysfunction resolved in 4 (0.9%) patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 3.0% (62/2086) (95%CI: 2.3%-3.8%) of patients developed immune-mediated nephritis and renal dysfunction. In the <RP2D/3D dose group (N=10), 2 patients who received serplulimab in combination with other monoclonal antibodies experienced immune-mediated nephritis and renal dysfunction. In the ≥RP2D/3D dose group (N=2 076), there were 9 patients who received serplulimab monotherapy, 42 patients who received serplulimab in combination with chemotherapy, and 9 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated nephritis and renal dysfunction. Among the patients experiencing immune-mediated nephritis and renal dysfunction, 0.5% (10/2086) of patients experienced serious adverse events and 2.5% (52/2086) of patients experienced non-serious adverse events. There were 1 (<0.1%) patient with Grade 4 immune-mediated nephritis and renal dysfunction, 6 (0.3%) patients with Grade 3 immune-mediated nephritis and renal dysfunction, 18 (0.9%) patients with Grade 2 immune-mediated nephritis and renal dysfunction, 37 (1.8%) patients with Grade 1 immune-mediated nephritis and renal dysfunction. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated nephritis and renal dysfunction was 2.83 months (range: 0.23 to 17.77 months). The median duration was 1.48 months (range: 0.13 to 17.94 months).<br><br>Serplulimab was discontinued in 0.2% (5/2086) of patients and temporarily discontinued in 0.6% (12/2086) of patients due to immune-mediated nephritis and renal dysfunction. Immune-mediated nephritis and renal dysfunction resolved in 30 (1.4%) patients at the time of data cut-off.<br><br><u>Post-Marketing Data Sources</u><br><br>As of 21Mar2025, 5 immune-mediated nephritis and renal dysfunction events (assessed by the company) were collected from post-marketing origin. |

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| | ***Immune-mediated endocrinopathies***<br><br>**Diabetes mellitus/hyperglycaemia**<br><br><u>Serplulimab in combination with carboplatin and etoposide in ES-SCLC</u><br><br>Diabetes mellitus/hyperglycaemia was observed in 2.1% (8/389) (95%CI: 0.9%-4.0%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 1.3% (5/389) of patients experienced serious adverse events and 0.8% (3/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 4 diabetes mellitus/hyperglycaemia, 5 (1.3%) patients with Grade 3 diabetes mellitus/hyperglycaemia, 2 (0.5%) patients with Grade 2 diabetes mellitus/hyperglycaemia. There was no patient with a fatal outcome.<br><br>The median time to onset of diabetes mellitus/hyperglycaemia was 4.71 months (range: 0.69 to 40.28 months). The median duration was 3.93 months (range: 0.53 to 10.68 months).<br><br>Serplulimab was discontinued in 0.3% (1/389) of patients and temporarily discontinued in 1.0% (4/389) of patients due to diabetes mellitus/hyperglycaemia. Diabetes mellitus/hyperglycaemia resolved in 1 (0.3%) patient at the time of data cut-off.<br><br><u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>Diabetes mellitus/hyperglycemia was observed in 0.4% (2/503) (95%CI: 0.0%-1.4%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.2% (1/503) of patients experienced serious adverse events and 0.2% (1/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 diabetes mellitus/hyperglycemia, 1 (0.2%) patient with Grade 1 diabetes mellitus/hyperglycemia. There was no patient with a fatal outcome.<br><br>The median time to onset of diabetes mellitus/hyperglycemia was 6.32 months (range: 4.34 to 8.31 months). The median duration was 5.31 months (range: 3.48 to 7.13 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/503) of patients due to diabetes mellitus/hyperglycemia. No diabetes mellitus/hyperglycemia resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Diabetes mellitus/hyperglycemia was observed in 0.8% (3/382) (95%CI: 0.2%-2.3%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.3% (1/382) of patients experienced serious |

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| | adverse events and 0.5% (2/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 4 diabetes mellitus/hyperglycemia, 2 (0.5%) patients with Grade 1 diabetes mellitus/hyperglycemia. There was no patient with a fatal outcome.<br><br>The median time to onset of diabetes mellitus/hyperglycemia was 3.71 months (range: 2.73 to 9.23 months). The median duration was 2.76 months (range: 2.04 to 3.48 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/382) of patients due to diabetes mellitus/hyperglycemia. Diabetes mellitus/hyperglycemia resolved in 2 (0.5%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Diabetes mellitus/hyperglycemia was observed in 0.9% (4/455) (95%CI: 0.2%-2.2%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.2% (1/455) of patients experienced serious adverse events and 0.7% (3/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 diabetes mellitus/hyperglycemia, and 3 (0.7%) patients with Grade 1 diabetes mellitus/hyperglycemia. There was no patient with a fatal outcome.<br><br>The median time to onset of diabetes mellitus/hyperglycemia was 7.46 months (range: 2.30 to 17.28 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to diabetes mellitus/hyperglycemia. No diabetes mellitus/hyperglycemia resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 0.9% (19/2086) (95%CI: 0.5%-1.4%) of patients experienced diabetes mellitus/hyperglycaemia. In the ≥RP2D/3D dose group (N=2 076), there were 2 patients who received serplulimab monotherapy, 16 patients who received serplulimab in combination with chemotherapy, and 1 patient who received serplulimab in combination with other monoclonal antibodies, experienced diabetes mellitus/hyperglycaemia. Among the patients experiencing diabetes mellitus/hyperglycaemia, 0.4% (9/2086) of patients experienced serious adverse events and 0.5% (10/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with Grade 4 diabetes mellitus/hyperglycaemia, 8 (0.4%) patients with Grade 3 diabetes mellitus/hyperglycaemia, 2 (<0.1%) patients with Grade 2 diabetes |

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| | mellitus/hyperglycaemia, 7 (0.3%) patients with Grade 1 diabetes mellitus/hyperglycaemia. There was no patient with a fatal outcome.<br><br>The median time to onset of diabetes mellitus/hyperglycaemia was 4.34 months (range: 0.69 to 40.28 months). The median duration was 3.48 months (range: 0.53 to 10.68 months).<br><br>Serplulimab was discontinued in <0.1% (1/2086) of patients and temporarily discontinued in 0.3% (7/2086) of patients due to diabetes mellitus/hyperglycaemia. Diabetes mellitus/ hyperglycaemia resolved in 3 (0.1%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 8 diabetes mellitus/hyperglycaemia events (assessed by the company) were collected from post-marketing origin.<br><br>**Thyroiditis**<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Thyroiditis was observed in 0.5% (2/389) (95%CI: 0.1%-1.8%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. These 2 patients experienced non-serious adverse events which were Grade 1. There was no patient with a fatal outcome.<br><br>The median time to onset of thyroiditis was 8.87 months (range: 4.67 to 13.08 months). The median duration was 11.30 months (range: 11.30 to 11.30 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in any patients due to thyroiditis. Thyroiditis resolved in 1 (0.3%) patient at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Thyroiditis was observed in 0.4% (2/503) (95%CI: 0.0%-1.4%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. Both patients experienced non-serious adverse events which were Grade 1. There was no patient with a fatal outcome.<br><br>The median time to onset of thyroiditis was 6.11 months (range: 1.38 to 10.84 months). The median duration was 1.20 months (range: 0.76 to 1.64 months). |

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| | Serplulimab was not temporarily discontinued/discontinued in any patients due to thyroiditis. No thyroiditis resolved in any patients at the time of data cut-off.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Thyroiditis was observed in 1.3% (5/382) (95%CI: 0.4%-3.0%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. All patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 2 thyroiditis, 4 (1.0%) patients with Grade 1 thyroiditis. There was no patient with a fatal outcome.<br><br>The median time to onset of thyroiditis was 8.02 months (range: 0.99 to 8.18 months). The median duration was 1.30 months (range: 1.08 to 1.51 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/382) of patients due to thyroiditis. Thyroiditis resolved in 2 (0.5%) patients at the time of data cut-off.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Thyroiditis was observed in 0.7% (3/455) (95%CI: 0.1%-1.9%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. All patients experienced non-serious adverse events which were Grade 2. There was no patient with a fatal outcome.<br><br>The median time to onset of thyroiditis was 6.64 months (range: 2.83 to 7.69 months). The median duration was 0.56 months (range: 0.56 to 0.56 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to thyroiditis. Thyroiditis resolved in 2 (0.4%) patients at the time of data cut-off.<br><br>Serplulimab in pooled safety set<br><br>Across clinical studies, 0.7% (15/2086) (95%CI: 0.4%-1.2%) of patients experienced thyroiditis. In the ≥RP2D/3D dose group (N=2 076), there were 4 patients who received serplulimab monotherapy, and 10 patients who received serplulimab in combination with chemotherapy, and 1 patient who received serplulimab in combination with other monoclonal antibodies, experienced thyroiditis. Among the patients experiencing thyroiditis, all patients experienced non-serious adverse events. There were 6 (0.3%) patients with Grade 2 thyroiditis, 9 (0.4%) patients with Grade 1 thyroiditis. There was no patient with a fatal outcome. |

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| | The median time to onset of thyroiditis was 6.64 months (range: 0.99 to 13.50 months). The median duration was 1.30 months (range: 0.56 to 11.30 months).<br><br>Serplulimab was temporarily discontinued in <0.1% (2/2086) of patients due to thyroiditis. Thyroiditis resolved in 5 (0.2%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 3 thyroiditis events (assessed by the company) were collected from post-marketing origin.<br><br>**Hyperthyroidism**<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Hyperthyroidism was observed in 10.8% (42/389) (95%CI: 7.9%-14.3%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. All patients experienced non-serious adverse events. There were 5 (1.3%) patients with Grade 2 hyperthyroidism, 37 (9.5%) patients with Grade 1 hyperthyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hyperthyroidism was 2.30 months (range: 1.31 to 31.18 months). The median duration was 1.41 months (range: 0.07 to 2.83 months).<br><br>Serplulimab was temporarily discontinued in 0.8% (3/389) of patients due to hyperthyroidism. Hyperthyroidism resolved in 31 (8.0%) patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Hyperthyroidism was observed in 8.2% (41/503) (95%CI: 5.9%-10.9%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. All patients experienced non-serious adverse events. There were 7 (1.4%) patients with Grade 2 hyperthyroidism, 34 (6.8%) patients with Grade 1 hyperthyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hyperthyroidism was 3.45 months (range: 0.62 to 27.50 months). The median duration was 1.61 months (range: 0.23 to 13.77 months).<br><br>Serplulimab was temporarily discontinued in 0.8% (4/503) of patients due to hyperthyroidism. No hyperthyroidism resolved in any patients at the time of data cut-off. |

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| | <u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Hyperthyroidism was observed in 5.5% (21/382) (95%CI: 3.4%-8.3%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. All patients experienced non-serious adverse events. There were 3 (0.8%) patients with Grade 2 hyperthyroidism, 18 (4.7%) patients with Grade 1 hyperthyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hyperthyroidism was 4.07 months (range: 0.89 to 10.61 months). The median duration was 1.58 months (range: 0.72 to 8.71 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/382) of patients due to hyperthyroidism. Hyperthyroidism resolved in 13 (3.4%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Hyperthyroidism was observed in 2.9% (13/455) (95%CI: 1.5%-4.8%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. All patients experienced non-serious adverse events. There were 2 (0.4%) patients with Grade 2 hyperthyroidism, and 11 (2.4%) patients with Grade 1 hyperthyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hyperthyroidism was 5.03 months (range: 1.31 to 19.52 months). The median duration was 2.00 months (range: 0.72 to 17.77 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to hyperthyroidism. Hyperthyroidism resolved in 7 (1.5%) patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 6.7% (139/2086) (95%CI: 5.6%-7.8%) of patients experienced hyperthyroidism. In the ≥RP2D/3D dose group (N=2 076), there were 15 patients who received serplulimab monotherapy, 99 patients who received serplulimab in combination with chemotherapy, and 25 patients who received serplulimab in combination with other monoclonal antibodies, experienced hyperthyroidism. Among the patients experiencing hyperthyroidism, all patients experienced non-serious adverse events. There were 21 (1.0%) patients with Grade 2 hyperthyroidism, and 118 (5.7%) patients with Grade 1 hyperthyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hyperthyroidism was 2.73 months (range: 0.62 to 31.18 months). The median duration was 1.45 months (range: 0.07 to 17.77 months). |

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| | Serplulimab was temporarily discontinued in 0.5% (10/2086) of patients due to hyperthyroidism. Hyperthyroidism resolved in 70 (3.4%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 7 hyperthyroidism events (assessed by the company) were collected from post-marketing origin.<br><br>**Hypothyroidism**<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Hypothyroidism was observed in 13.1% (51/389) (95%CI: 9.9%-16.9%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 0.3% (1/389) of patients experienced serious adverse events and 12.9% (50/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 3 hypothyroidism, 23 (5.9%) patients with Grade 2 hypothyroidism, 27 (6.9%) patients with Grade 1 hypothyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hypothyroidism was 3.58 months (range: 1.38 to 34.10 months). The median duration was 2.73 months (range: 0.69 to 7.49 months).<br><br>Serplulimab was temporarily discontinued in 1.8% (7/389) of patients due to hypothyroidism. Hypothyroidism resolved in 25 (6.4%) patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Hypothyroidism was observed in 11.5% (58/503) (95%CI: 8.9%-14.7%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.2% (1/503) of patients experienced serious adverse events and 11.3% (57/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 hypothyroidism, 25 (5.0%) patients with Grade 2 hypothyroidism, 32 (6.4%) patients with Grade 1 hypothyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hypothyroidism was 3.79 months (range: 1.25 to 25.17 months). The median duration was 2.40 months (range: 0.13 to 29.08 months).<br><br>Serplulimab was discontinued in 0.2% (1/503) of patients and temporarily discontinued in 1.6% (8/503) of patients due to |

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| | hypothyroidism. Hypothyroidism resolved in 8 (1.6%) patients at the time of data cut-off.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Hypothyroidism was observed in 12.3% (47/382) (95%CI: 9.2%-16.0%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.5% (2/382) of patients experienced serious adverse events and 11.8% (45/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 3 hypothyroidism, 20 (5.2%) patients with Grade 2 hypothyroidism, 26 (6.8%) patients with Grade 1 hypothyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hypothyroidism was 3.42 months (range: 0.46 to 21.65 months). The median duration was 2.46 months (range: 0.46 to 11.07 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in any patients due to hypothyroidism. Hypothyroidism resolved in 26 (6.8%) patients at the time of data cut-off.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Hypothyroidism was observed in 8.1% (37/455) (95%CI: 5.8%-11.0%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.2% (1/455) of patients experienced serious adverse events and 7.9% (36/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 hypothyroidism, 22 (4.8%) patients with Grade 2 hypothyroidism, and 14 (3.1%) patients with Grade 1 hypothyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hypothyroidism was 6.24 months (range: 0.89 to 18.20 months). The median duration was 4.01 months (range: 0.95 to 13.11 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to hypothyroidism. Hypothyroidism resolved in 13 (2.9%) patients at the time of data cut-off.<br><br>Serplulimab in pooled safety set<br><br>Across clinical studies, 11.7% (244/2086) (95%CI: 10.3%-13.2%) of patients experienced hypothyroidism. In the ≥RP2D/3D dose group (N=2 076), there were 33 patients who received serplulimab monotherapy, 161 patients who received serplulimab in combination with chemotherapy, and 50 patients who received serplulimab in combination with other monoclonal antibodies, experienced hypothyroidism. Among the patients experiencing hypothyroidism, 0.2% (5/2086) of patients experienced serious adverse events and |

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| | 11.5% (239/2086) of patients experienced non-serious adverse events. There were 4 (0.2%) patients with Grade 3 hypothyroidism, 117 (5.6%) patients with Grade 2 hypothyroidism, 123 (5.9%) patients with Grade 1 hypothyroidism. There was no patient with a fatal outcome.<br><br>The median time to onset of hypothyroidism was 3.83 months (range: 0.46 to 34.10 months). The median duration was 2.73 months (range: 0.13 to 29.08 months).<br><br>Serplulimab was discontinued in <0.1% (1/2086) and temporarily discontinued in 0.9% (19/2086) of patients due to hypothyroidism. Hypothyroidism resolved in 89 (4.3%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 11 hypothyroidism events (assessed by the company) were collected from post-marketing origin.<br><br>**Pituitary disorders**<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Pituitary disorders were observed in 0.8% (3/389) (95%CI: 0.2%-2.2%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. Among the patients experiencing pituitary disorders, all patients experienced non-serious adverse events. There were 2 (0.5%) patients with Grade 2 pituitary disorders, 1 (0.3%) patient with Grade 1 pituitary disorders. There was no patient with a fatal outcome.<br><br>The median time to onset of pituitary disorders was 6.97 months (range: 6.47 to 20.53 months).<br><br>Serplulimab was discontinued in 0.3% (1/389) of patients due to pituitary disorders. Pituitary disorders resolved in 2 (0.5%) patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Pituitary disorders were not observed in patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Pituitary disorders were observed in 1.3% (5/382) (95%CI: 0.4%-3.0%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.8% |

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| | (3/382) of patients experienced serious adverse events and 0.5% (2/382) of patients experienced non-serious adverse events. There were 4 (1.0%) patients with Grade 2 pituitary disorders, 1 (0.3%) patient with Grade 1 pituitary disorders. There was no patient with a fatal outcome.<br><br>The median time to onset of pituitary disorders was 6.21 months (range: 1.68 to 19.84 months). The duration was 3.25 months (range: 3.25 to 3.25 months).<br><br>Serplulimab was discontinued in 0.3% (1/382) of patients and temporarily discontinued in 0.3% (1/382) of patients due to pituitary disorders. Pituitary disorders resolved in 2 (0.5%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Pituitary disorders were observed in 1.1% (5/455) (95%CI: 0.4%-2.5%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.4% (2/455) of patients experienced serious adverse events and 0.7% (3/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 3 pituitary disorders, 3 (0.7%) patients with Grade 2 pituitary disorders, and 1 (0.2%) patient with Grade 1 pituitary disorders. There was no patient with a fatal outcome.<br><br>The median time to onset of pituitary disorders was 7.03 months (range: 5.39 to 7.59 months).<br><br>Serplulimab was discontinued in 0.2% (1/455) of patients and temporarily discontinued in 0.7% (3/455) of patients due to pituitary disorders. No pituitary disorders resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 0.8% (16/2086) (95%CI: 0.4%-1.2%) of patients experienced pituitary disorders. In the ≥RP2D/3D dose group (N=2 076), there were 13 patients who received serplulimab in combination with chemotherapy, and 3 patients who received serplulimab in combination with other monoclonal antibodies, experienced pituitary disorders. Among the patients experiencing pituitary disorders, 0.3% (6/2086) of patients experienced serious adverse events and 0.5% (10/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with Grade 3 pituitary disorders, 10 (0.5%) patients with Grade 2 pituitary disorders, 4 (0.2%) patients with Grade 1 pituitary disorders. There was no patient with a fatal outcome. |

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| | The median time to onset of pituitary disorders was 6.72 months (range: 1.41 to 20.53 months). The median duration was 3.25 months (range: 3.25 to 3.25 months).<br><br>Serplulimab was discontinued in 0.1% (3/2086) of patients and temporarily discontinued in 0.3% (6/2086) of patients due to pituitary disorders. Pituitary disorders resolved in 5 (0.2%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 1 pituitary disorders event (assessed by the company) was collected from post-marketing origin.<br><br>**Adrenal gland disorders**<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Adrenal gland disorders were observed in 0.5% (2/389) (95%CI: 0.1%-1.8%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. These 2 patients experienced non-serious adverse events which were Grade 2. There was no patient with a fatal outcome.<br><br>The median time to onset of adrenal gland disorders was 6.34 months (range: 5.75 to 6.93 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/389) of patients due to adrenal gland disorders. No adrenal gland disorders resolved in any patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Adrenal gland disorders were observed in 1.0% (5/503) (95%CI: 0.3%-2.3%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. All patients experienced non-serious adverse events which were Grade 2. There was no patient with a fatal outcome.<br><br>The median time to onset of adrenal gland disorders was 11.79 months (range: 3.55 to 21.45 months). The median duration was 4.60 months (range: 4.60 to 4.60 months).<br><br>Serplulimab was discontinued in 0.8% (4/503) of patients due to adrenal gland disorders. Adrenal gland disorders resolved in 1 (0.2%) patient at the time of data cut-off.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Adrenal gland disorders were observed in 0.8% (3/382) (95%CI: 0.2%-2.3%) of patients with OSCC treated with serplulimab in |

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| | combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.3% (1/382) of patients experienced serious adverse events and 0.5% (2/382) of patients experienced non-serious adverse events. There were 2 (0.5%) patients with Grade 3 adrenal gland disorders, 1 (0.3%) patient with Grade 1 adrenal gland disorders. There was no patient with a fatal outcome.<br><br>The median time to onset of adrenal gland disorders was 6.24 months (range: 5.39 to 11.53 months).<br><br>Serplulimab was temporarily discontinued in 0.5% (2/382) of patients due to adrenal gland disorders. Adrenal gland disorders resolved in 2 (0.5%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Adrenal gland disorders were observed in 0.2% (1/455) (95%CI: 0.0%-1.2%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. The patient experienced non-serious adverse event which was Grade 2. There was no patient with a fatal outcome.<br><br>The median time to onset of adrenal gland disorders was 5.78 months (range: 5.78 to 5.78 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in any patients due to adrenal gland disorders. No adrenal gland disorders resolved in any patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 0.5% (11/2086) (95%CI: 0.3%-0.9%) of patients developed adrenal gland disorders. In the ≥RP2D/3D dose group (N=2 076), there were 9 patients who received serplulimab in combination with chemotherapy, and 2 patients who received serplulimab in combination with other monoclonal antibodies, experienced adrenal gland disorders. Among the patients experiencing adrenal gland disorders, <0.1% (1/2086) of patients experienced serious adverse events and 0.5% (10/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with Grade 3 adrenal gland disorders, 8 (0.4%) patients with Grade 2 adrenal gland disorders, 1 (<0.1%) patient with Grade 1 adrenal gland disorders. There was no patient with a fatal outcome.<br><br>The median time to onset of adrenal gland disorders was 6.24 months (range: 3.55 to 21.45 months). The median duration was 4.60 months (range: 4.60 to 4.60 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (7/2086) of patients due to adrenal gland disorders. Adrenal gland disorders resolved in 3 (0.1%) patients at the time of data cut-off. |

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| | Post-Marketing Data Sources<br><br>As of 21Mar2025, 5 adrenal gland disorders events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated skin adverse reactions***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated skin adverse reactions were observed in 7.5% (29/389) (95%CI: 5.0%-10.5%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 0.3% (1/389) of patients experienced serious adverse events and 7.2% (28/389) of patients experienced non-serious adverse events. There were 2 (0.5%) patients with Grade 3 immune-mediated skin adverse reactions, 12 (3.1%) patients with Grade 2 immune-mediated skin adverse reactions, 15 (3.9%) patients with Grade 1 immune-mediated skin adverse reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated skin adverse reactions was 3.84 months (range: 0.23 to 30.52 months). The median duration was 0.99 months (range: 0.13 to 10.41 months).<br><br>Serplulimab was discontinued in 0.8% (3/389) of patients and temporarily discontinued in 1.5% (6/389) of patients due to immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions resolved in 15 (3.9%) patients at the time of data cut-off.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Immune-mediated skin adverse reactions were observed in 5.0% (25/503) (95%CI: 3.2%-7.2%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 0.2% (1/503) of patients experienced serious adverse events and 4.8% (24/503) of patients experienced non-serious adverse events. There were 3 (0.6%) patients with Grade 3 immune-mediated skin adverse reactions, 12 (2.4%) patients with Grade 2 immune-mediated skin adverse reactions, 10 (2.0%) patients with Grade 1 immune-mediated skin adverse reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated skin adverse reactions was 7.00 months (range: 0.23 to 19.22 months). The median duration was 2.48 months (range: 0.07 to 9.99 months).<br><br>Serplulimab was discontinued in 0.2% (1/503) of patients and temporarily discontinued in 1.8% (9/503) of patients due to immune-mediated skin adverse reactions. Immune-mediated skin |

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| | adverse reactions resolved in 3 (0.6%) patients at the time of data cut-off.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Immune-mediated skin adverse reactions were observed in 8.1% (31/382) (95%CI: 5.6%-11.3%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 0.8% (3/382) of patients experienced serious adverse events and 7.3% (28/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with a fatal outcome, 1 (0.3%) patient with Grade 4 immune-mediated skin adverse reactions, 5 (1.3%) patients with Grade 3 immune-mediated skin adverse reactions, 9 (2.4%) patients with Grade 2 immune-mediated skin adverse reactions, and 15 (3.9%) patients with Grade 1 immune-mediated skin adverse reactions.<br><br>The median time to onset of immune-mediated skin adverse reactions was 2.96 months (range: 0.07 to 18.92 months). The median duration was 2.07 months (range: 0.07 to 8.31 months).<br><br>Serplulimab was discontinued in 1.0% (4/382) of patients and temporarily discontinued in 2.4% (9/382) of patients due to immune-mediated skin reactions. Immune-mediated skin adverse reactions resolved in 14 (3.7%) patients at the time of data cut-off.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Immune-mediated skin adverse reactions were observed in 8.8% (40/455) (95%CI: 6.4%-11.8%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 1.5% (7/455) of patients experienced serious adverse events and 7.3% (33/455) of patients experienced non-serious adverse events. There were 6 (1.3%) patients with Grade 3 immune-mediated skin adverse reactions, 16 (3.5%) patients with Grade 2 immune-mediated skin adverse reactions, and 18 (4.0%) patients with Grade 1 immune-mediated skin adverse reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated skin adverse reactions was 1.17 months (range: 0.03 to 17.91 months). The median duration was 0.79 months (range: 0.10 to 19.06 months).<br><br>Serplulimab was discontinued in 0.4% (2/455) of patients and temporarily discontinued in 1.8% (8/455) of patients due to immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions resolved in 28 (6.2%) patients at the time of data cut-off. |

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| | Serplulimab in pooled safety set<br><br>Across clinical studies, 7.8% (162/2086) (95%CI: 6.7%-9.0%) of patients experienced immune-mediated skin adverse reactions. In the <RP2D/3D dose group (N=10), there were 1 patient who received monotherapy, and 1 patient who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated skin adverse reactions. In the ≥RP2D/3D dose group (N=2 076), there were 20 patients who received serplulimab monotherapy, 107 patients who received serplulimab in combination with chemotherapy, and 33 patients who received serplulimab in combination with other monoclonal antibodies, experienced immune-mediated skin adverse reactions. Among the patients experiencing immune-mediated skin adverse reactions, 0.7% (14/2086) of patients experienced serious adverse events and 7.1% (148/2086) of patients experienced non-serious adverse events. There were 1 (<0.1%) patient with a fatal outcome, 1 (<0.1%) patient with Grade 4 immune-mediated skin adverse reactions, 17 (0.8%) patients with Grade 3 immune-mediated skin adverse reactions, 63 (3.0%) patients with Grade 2 immune-mediated skin adverse reactions, 80 (3.8%) patients with Grade 1 immune-mediated skin adverse reactions.<br><br>The median time to onset of immune-mediated skin adverse reactions was 2.96 months (range: 0.03 to 30.52 months). The median duration was 1.56 months (range: 0.07 to 19.06 months).<br><br>Serplulimab was discontinued in 0.5% (10/2086) of patients and temporarily discontinued in 1.6% (33/2086) of patients due to immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions resolved in 89 (4.3%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 25 immune-mediated skin adverse reactions events (assessed by the company) were collected from post-marketing origin.<br><br>***Immune-mediated uveitis***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Immune-mediated uveitis was not observed in patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301.<br><br>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC<br><br>Immune-mediated uveitis was not observed in patients with non-squamous NSCLC treated with serplulimab in combination with |

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| | chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301.<br><br>Serplulimab in combination with cisplatin and 5-FU in OSCC<br><br>Immune-mediated uveitis was not observed in patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301.<br><br>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC<br><br>Immune-mediated uveitis was not observed in patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303.<br><br>Serplulimab in pooled safety set<br><br>Across clinical studies, <0.1% (1/2086) (95%CI: 0.0%-0.3%) of patients developed immune-mediated uveitis. In the ≥RP2D/3D dose group (N=2 076), the patient who received serplulimab monotherapy had immune-mediated uveitis. The patient experienced non-serious adverse event which was Grade 1. There was no patient with a fatal outcome.<br><br>The median time to onset of immune-mediated uveitis was 6.90 months (range: 6.90 to 6.90 months). The median duration was 1.35 months (range: 1.35 to 1.35 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in the patient due to immune-mediated uveitis. Immune-mediated uveitis resolved in 1 (<0.1%) patient at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, no immune-mediated uveitis event was collected from post-marketing origin.<br><br>***Other immune-mediated adverse reactions***<br><br>Serplulimab in combination with carboplatin and etoposide in ES-SCLC<br><br>Other immune-mediated adverse reactions were observed in 19.0% (74/389) (95%CI: 15.2%-23.3%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 4.6% (18/389) of patients experienced serious adverse events and 14.4% (56/389) of patients experienced non-serious adverse events. There were 5 (1.3%) patients with fatal outcomes, 6 (1.5%) patients with Grade 4 other immune-mediated adverse reactions, 8 (2.1%) patients with Grade 3 other immune-mediated adverse reactions, 21 (5.4%) patients |

with Grade 2 other immune-mediated adverse reactions, 34 (8.7%) patients with Grade 1 other immune-mediated adverse reactions.

The median time to onset of other immune-mediated adverse reactions was 2.46 months (range: 0.07 to 49.35 months). The median duration was 0.79 months (range: 0.03 to 18.99 months).

Serplulimab was discontinued in 2.8% (11/389) of patients and temporarily discontinued in 3.1% (12/389) of patients due to other immune-mediated adverse reactions. Other immune-mediated adverse reactions resolved in 33 (8.5%) patients at the time of data cut-off.

Other immune-mediated adverse reactions meeting the criteria of incidence ≥1%, or ≥ CTCAE Grade 3, or leading to serplulimab withdraw listed as follows.

| **SOC** | **PT (Incidence with all Grades)** |
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| Investigations | Platelet count decreased (1.5%), white blood cell count decreased (1.3%), blood alkaline phosphatase increased (1.0%), neutrophil count decreased (1.0%), troponin increased (0.5%), cortisol decreased (0.3%), blood cholesterol increased (0.3%) |
| General disorders and administration site conditions | Malaise (2.1%), asthenia (1.3%), fatigue (1.3%), pyrexia (0.8%) |
| Metabolism and nutrition disorders | Decreased appetite (1.3%) |
| Blood and lymphatic system disorders | Anaemia (2.8%), leukopenia (0.5%), thrombocytopenia (0.3%), neutropenia (0.3%) |
| Cardiac disorders | Acute coronary syndrome (0.3%), acute myocardial infarction (0.3%), cardiac failure acute (0.3%) |
| Gastrointestinal disorders | Vomiting (0.3%), Gastric ulcer (0.3%) |
| Nervous system disorders | Immune-mediated encephalitis (0.5%), neuropathy peripheral (0.5%), encephalitis autoimmune (0.3%), peripheral sensorimotor neuropathy (0.3%) |
| Infections and infestations | Sepsis (0.3%) |
| Respiratory, thoracic and mediastinal disorders | Chronic obstructive pulmonary disease (0.3%) |
| Psychiatric disorders | Panic disorder (0.3%) |
| Eye disorders | Vision blurred (0.3%) |

Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC

Other immune-mediated adverse reactions were observed in 7.4% (37/503) (95%CI: 5.2%-10.0%) of patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. 3.2% (16/503) of patients experienced serious adverse events and 4.2% (21/503) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with a fatal outcome, 2 (0.4%) patients with Grade 4 other immune-mediated adverse reactions, 10 (2.0%) patients with Grade 3 other immune-mediated adverse reactions, 12 (2.4%) patients with Grade 2 other immune-mediated adverse reactions, 12 (2.4%) patients with Grade 1 other immune-mediated adverse reactions.

The median time to onset of other immune-mediated adverse reactions was 4.07 months (range: 0.13 to 23.69 months). The median duration was 0.71 months (range: 0.10 to 13.90 months).

Serplulimab was discontinued in 1.0% (5/503) of patients and temporarily discontinued in 3.8% (19/503) of patients due to other immune-mediated adverse reactions. Other immune-mediated adverse reactions resolved in 7 (1.4%) patients at the time of data cut-off.

Other immune-mediated adverse reactions meeting the criteria of incidence ≥1%, or ≥CTCAE Grade 3, or leading to serplulimab withdraw listed as follows.

| **SOC** | **PT (Incidence with all Grades)** |
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| Investigations | N-terminal prohormone brain natriuretic peptide increased (1.0%), troponin I increased (0.8%), platelet count decreased (0.6%) |
| General disorders and administration site conditions | Asthenia (0.8%) |
| Renal and urinary disorders | Chronic kidney disease (0.6%), urinary tract inflammation (0.2%) |
| Cardiac disorders | Cardiac failure (0.2%) |
| Infections and infestations | Peritonitis (0.2%) |
| Metabolism and nutrition disorders | Decreased appetite (0.2%) |
| Nervous system disorders | Epilepsy (0.2%) |
| Psychiatric disorders | Abnormal behaviour (0.2%) |
| Respiratory, thoracic and | Chronic obstructive pulmonary disease (0.2%) |

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| mediastinal disorders | |

Serplulimab in combination with cisplatin and 5-FU in OSCC

Other immune-mediated adverse reactions were observed in 9.7% (37/382) (95%CI: 6.9%-13.1%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. 2.6% (10/382) of patients experienced serious adverse events and 7.1% (27/382) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with a fatal outcome, 2 (0.5%) patients with Grade 4 other immune-mediated adverse reactions, 7 (1.8%) patients with Grade 3 other immune-mediated adverse reactions, 12 (3.1%) patients with Grade 2 other immune-mediated adverse reactions, and 15 (3.9%) patients with Grade 1 other immune-mediated adverse reactions.

The median time to onset of other immune-mediated adverse reactions was 2.69 months (range: 0.33 to 20.50 months). The median duration was 0.56 months (range: 0.03 to 7.43 months).

Serplulimab was discontinued in 1.0% (4/382) of patients and temporarily discontinued in 3.1% (12/382) of patients due to other immune-mediated adverse reactions. Other immune-mediated adverse reactions resolved in 20 (5.2%) patients at the time of data cut-off.

Other immune-mediated adverse reactions meeting the criteria of incidence ≥1%, or ≥CTCAE Grade 3, or leading to serplulimab withdraw listed as follows.

| **SOC** | **PT (Incidence with all Grades)** |
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| Investigations | Neutrophil count decreased (1.0%), platelet count decreased (1.0%), blood alkaline phosphatase increased (0.3%), blood creatine phosphokinase increased (0.3%), cardiac function test abnormal (0.3%) |
| Blood and lymphatic system disorders | Anaemia (0.8%) |
| Gastrointestinal disorders | Abdominal pain (0.3%), mouth ulceration (0.3%), upper gastrointestinal haemorrhage (0.3%) |
| General disorders and administration site conditions | Pyrexia (0.8%) |
| Metabolism and nutrition disorders | Decreased appetite (0.5%) |
| Cardiac disorders | Ventricular extrasystoles (0.3%) |
| Infections and infestations | Septic shock (0.3%) |

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| Nervous system disorders | Immune-mediated neuropathy (0.3%) |

Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC

Other immune-mediated adverse reactions were observed in 11.0% (50/455) (95%CI: 8.3%-14.2%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 2.6% (12/455) of patients experienced serious adverse events and 8.4% (38/455) of patients experienced non-serious adverse events. There were 2 (0.4%) patients with fatal outcomes, 7 (1.5%) patients with Grade 4 other immune-mediated adverse reactions, 8 (1.8%) patients with Grade 3 other immune-mediated adverse reactions, 12 (2.6%) patients with Grade 2 other immune-mediated adverse reactions, and 21 (4.6%) patients with Grade 1 other immune-mediated adverse reactions.

The median time to onset of other immune-mediated adverse reactions was 7.10 months (range: 0.03 to 31.61 months). The median duration was 0.82 months (range: 0.03 to 15.70 months).

Serplulimab was discontinued in 2.0% (9/455) of patients and temporarily discontinued in 4.0% (18/455) of patients due to other immune-mediated adverse reactions. Other immune-mediated adverse reactions resolved in 25 (5.5%) patients at the time of data cut-off.

Other immune-mediated adverse reactions meeting the criteria of incidence ≥1%, or ≥CTCAE Grade 3, or leading to serplulimab withdraw listed as follows.

| **SOC** | **PT (Incidence with all Grades)** |
|---|---|
| Investigations | Platelet count decreased (1.3%), neutrophil count decreased (0.9%), white blood cell count decreased (0.7%) |
| Blood and lymphatic system disorders | Leukopenia (0.7%), anaemia (0.4%), thrombocytopenia (0.4%), immune thrombocytopenia (0.2%) |
| Metabolism and nutrition disorders | Hypomagnesaemia (0.7%), hypokalaemia (0.4%), electrolyte imbalance (0.2%) |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea (0.4%), respiratory failure (0.2%) |
| Cardiac disorders | Cardiotoxicity (0.2%), myocardial infarction (0.2%) |

| | |
|---|---|
| Eye disorders | Glaucoma (0.2%), vision blurred (0.2%) |
| Nervous system disorders | Dizziness (0.2%), encephalopathy (0.2%) |
| Ear and labyrinth disorders | Tinnitus (0.2%) |
| General disorders and administration site conditions | Asthenia (0.2%) |
| Musculoskeletal and connective tissue disorders | Joint swelling (0.2%), pain in extremity (0.2%) |
| Renal and urinary disorders | Chronic kidney disease (0.2%) |

Serplulimab in pooled safety set

Across clinical studies, 13.0% (272/2086) (95%CI: 11.6%-14.6%) of patients experienced other immune-mediated adverse reactions. In the <RP2D/3D dose group (N=10), there were 1 patient who received serplulimab monotherapy, and 3 patients who received serplulimab in combination with other monoclonal antibodies, experienced other immune-mediated adverse reactions. In the ≥RP2D/3D dose group (N=2 076), there were 41 patients who received serplulimab monotherapy, 168 patients who received serplulimab in combination with chemotherapy, and 59 patients who received serplulimab in combination with other monoclonal antibodies, experienced other immune-mediated adverse reactions. Among the patients experiencing other immune-mediated adverse reactions, 3.1% (65/2086) of patients experienced serious adverse events and 9.9% (207/2086) of patients experienced non-serious adverse events. There were 11 (0.5%) patients with fatal outcomes, 18 (0.9%) patients with Grade 4 other immune-mediated adverse reactions, 45 (2.2%) patients with Grade 3 other immune-mediated adverse reactions, 74 (3.5%) patients with Grade 2 other immune-mediated adverse reactions, 124 (5.9%) patients with Grade 1 other immune-mediated adverse reactions.

The median time to onset of other immune-mediated adverse reactions was 3.12 months (range: 0.03 to 49.35 months). The median duration was 0.89 months (range: 0.03 to 18.99 months).

Serplulimab was discontinued in 1.5% (32/2086) of patients and temporarily discontinued in 3.7% (78/2086) of patients due to other immune-mediated adverse reactions. Other immune-mediated adverse reactions resolved in 127 (6.1%) patients at the time of data cut-off.

Other immune-mediated adverse reactions meeting the criteria of incidence ≥1%, or ≥ CTCAE Grade 3, or leading to serplulimab withdraw listed as follows.

| SOC | PT (Incidence with all Grades) |
|---|---|
| Investigations | Platelet count decreased (1.4%), white blood cell count decreased (0.9%), blood alkaline phosphatase increased (0.8%), neutrophil count decreased (0.8%), blood creatine phosphokinase increased (0.6%), cortisol decreased (0.5%), blood lactate dehydrogenase increased (0.4%), N-terminal prohormone brain natriuretic peptide increased (0.3%), troponin I increased (0.2%), troponin increased (0.1%), blood cholesterol increased (<0.1%), cardiac function test abnormal (<0.1%) |
| General disorders and administration site conditions | Asthenia (0.8%), pyrexia (0.5%), fatigue (0.4%) |
| Metabolism and nutrition disorders | Decreased appetite (0.5%), hypokalaemia (0.1%), hyponatraemia (0.1%), hypomagnesaemia (0.1%), electrolyte imbalance (<0.1%) |
| Blood and lymphatic system disorders | Anaemia (0.9%), leukopenia (0.2%), thrombocytopenia (0.1%), neutropenia (<0.1%), immune thrombocytopenia (<0.1%) |
| Cardiac disorders | Ventricular extrasystoles (0.3%), acute coronary syndrome (<0.1%), acute myocardial infarction (<0.1%), cardiac failure (<0.1%), cardiac failure acute (<0.1%), cardiotoxicity (<0.1%), myocardial infarction (<0.1%) |
| Gastrointestinal disorders | Abdominal pain (0.2%), vomiting (0.2%), mouth ulceration (0.1%), gastric ulcer (<0.1%), proctitis (<0.1%), upper gastrointestinal haemorrhage (<0.1%) |
| Nervous system disorders | Dizziness (<0.1%), immune-mediated encephalitis (<0.1%), neuropathy peripheral (<0.1%), encephalitis autoimmune (<0.1%), encephalopathy (<0.1%), epilepsy (<0.1%), immune-mediated neuropathy (<0.1%), peripheral sensorimotor neuropathy (<0.1%) |
| Musculoskeletal and connective tissue disorders | Muscular weakness (0.2%), pain in extremity (<0.1%), joint swelling (<0.1%) |
| Renal and urinary disorders | Chronic kidney disease (0.2%), urinary tract inflammation (<0.1%) |

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| | <table><tr><td>Infections and infestations</td><td>Sepsis (<0.1%), peritonitis (<0.1%), septic shock (<0.1%)</td></tr><tr><td>Respiratory, thoracic and mediastinal disorders</td><td>Dyspnoea (0.1%), respiratory failure (<0.1%), chronic obstructive pulmonary disease (<0.1%)</td></tr><tr><td>Psychiatric disorders</td><td>Panic disorder (<0.1%), abnormal behaviour (<0.1%)</td></tr><tr><td>Eye disorders</td><td>Vision blurred (<0.1%), glaucoma (<0.1%)</td></tr><tr><td>Ear and labyrinth disorders</td><td>Tinnitus (<0.1%)</td></tr><tr><td>Hepatobiliary disorders</td><td>Cholangitis acute (<0.1%)</td></tr></table><br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 44 other immune-mediated adverse reactions events (assessed by the company) were collected from post-marketing origin. Arthritis, immune-mediated cystitis, immune-mediated encephalitis, immune-mediated myositis, muscular weakness, myasthenia gravis and myocardial injury were collected more than once. |
| Risk factors and risk groups: | No analysis of specific risk factors associated with immune-mediated adverse reactions has been performed. There are no known risk factors for patients treated with serplulimab developing immune-mediated adverse reactions. |
| Preventability: | Immune-mediated myocarditis, including fatal cases, has been reported in patients receiving serplulimab. 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.<br><br>Immune-mediated pancreatitis, including increases in serum amylase and lipase levels and fatal cases, has been reported in |

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| | patients receiving serplulimab. 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.<br><br>Immune-mediated lung disease, including fatal cases, has been reported in patients receiving serplulimab. Patients should be monitored for signs and symptoms of immune-mediated lung disease such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Suspected immune-mediated lung disease should be confirmed with radiographic imaging, and other causes excluded. Serplulimab should be withheld for Grade 2 immune-mediated lung disease until adverse reactions recover or improve to Grade 1. And permanently discontinued for Grade 3 or 4 or recurrent Grade 2 immune-mediated lung disease.<br><br>Immune-mediated colitis, including fatal cases, has been reported in patients receiving serplulimab. 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-related aetiologies should be ruled out. Serplulimab should be withheld for Grade 2 or 3 colitis until adverse reactions recover or improve to Grade 1. And permanently discontinued for Grade 4 or recurrent Grade 3 colitis. The potential risk of gastrointestinal perforation should be taken into consideration and confirmed by radiographic imaging and/or endoscopy if necessary.<br><br>Immune-mediated hepatitis, including fatal cases, has been reported in patients receiving serplulimab. 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. Serplulimab should be withheld for Grade 2 with AST or ALT >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN until adverse reactions recover or improve to Grade 1. And permanently discontinued for Grade 3 or 4 with AST or ALT >5 times ULN, or total bilirubin >3 times ULN.<br><br>Immune-mediated nephritis and renal insufficiency has been reported in patients receiving serplulimab. 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 |

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| | patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out. Serplulimab should be withheld for Grade 2 elevation of serum creatinine until adverse reactions recover or improve to Grade 1. And permanently discontinued for Grade 3 or 4 elevation of serum creatinine.<br><br>Hyperglycaemia or type 1 diabetes mellitus has been reported in patients receiving serplulimab. 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.<br><br>Thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis have been reported in patients receiving serplulimab. 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.<br><br>Hypophysitis has been reported in patients receiving serplulimab. 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.<br><br>Adrenal insufficiency has been reported in patients receiving serplulimab. 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 |

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| | monitored continuously to ensure appropriate hormone replacement.<br><br>Immune-mediated skin adverse reactions have been reported in patients receiving serplulimab. 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.<br><br>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.<br><br>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. |
| Impact on the risk-benefit balance of the product: | Immune-mediated adverse reactions may be life-threatening or fatal in individual patients. Serplulimab has shown be effective in the following studies: Serplulimab combined with carboplatin and etoposide for treatment of adult patients with ES-SCLC; Serplulimab combined with chemotherapy (carboplatin and pemetrexed) and/or HLX04 for the treatment of adult patients with non-squamous NSCLC; Serplulimab combined with cisplatin and 5-FU for the treatment of adult patients with OSCC; Serplulimab monotherapy or serplulimab combined with carboplatin and nab-paclitaxel in squamous NSCLC. Overall the benefit of serplulimab in combination with chemotherapy for treating a life-threatening condition is considered to outweigh the risk of the important identified risk that can be managed in clinical practice through monitoring to prevent serious complications.<br><br>The important identified risk will be further monitored and characterised in patients exposed to serplulimab in the ongoing clinical trials and during post-marketing activities. |
| Public health impact: | Serplulimab can be obtained only via prescription and will not be supposedly used outside the controlled environment. The warnings of drug adverse reactions and the recommended dose modifications for the adverse reactions are included in the SmPC. The potential impact on public health is considered to be low. |

| **Important Identified Risk:** Severe infusion reactions | |
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| Potential mechanisms: | Infusion-related reactions are generally caused by the release of cytokines and/or other chemical mediators. However, allergic reaction or hypersensitivity to protein may also cause infusion-related reactions in some patients. |
| Evidence source(s) and strength of evidence: | <u>Serplulimab in combination with carboplatin and etoposide in ES-SCLC</u><br><br>The safety of serplulimab in combination with carboplatin and etoposide was evaluated in the pivotal study HLX10-005-SCLC301 (389 patients). Severe infusion reactions were observed in patients treated with serplulimab in this clinical trial.<br><br><u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>The safety of serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 was evaluated in the pivotal study HLX10-002-NSCLC301 (503 patients). Infusion reactions were observed in patients treated with serplulimab in this clinical trial.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>The safety of serplulimab in combination with cisplatin and 5-FU was evaluated in the pivotal study HLX10-007-EC301 (382 patients). Infusion reactions were observed in patients treated with serplulimab in this clinical trial.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>The safety of serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel was evaluated in the pivotal study HLX10-004-NSCLC303 (455 patients). Infusion reactions were observed in patients treated with serplulimab in this clinical trial.<br><br><u>Serplulimab in pooled safety set</u><br><br>The safety of serplulimab in the pivotal studies: HLX10-005-SCLC301 (patient: 389) for ES-SCLC, HLX10-002-NSCLC301 (patient: 503) for non-squamous NSCLC, HLX10-007-EC301 (patient: 382) for OSCC, HLX10-004-NSCLC303 (patient: 455) for squamous NSCLC; in the clinical trials with serplulimab single agent: HLX10-010-MSI201 (patient: 108), HLX10-001 (patient: 66), HLX10-008-HCC201 (patient: 21); in the clinical trials with combined chemotherapy: HLX10-011-CC201 (patient: 21); and in the clinical trials with combined other monoclonal antibodies: HLX10HLX04-001 (patient: 26), HLX10-008-HCC201 (patient: 102), HLX10HLX07-001 (patient: 13) was evaluated. Severe infusion reactions were observed in patients treated with serplulimab in these clinical trials. |

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| Characterisation of the risk: | <u>Serplulimab in combination with carboplatin and etoposide in ES-SCLC</u><br><br>Infusion reactions were observed in 2.1% (8/389) (95%CI: 0.9%-4.0%) of patients with ES-SCLC treated with serplulimab in combination with carboplatin and etoposide in pivotal study HLX10-005-SCLC301. 0.5% (2/389) of patients experienced serious adverse events and 1.5% (6/389) of patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 4 severe infusion reactions, 1 (0.3%) patient with Grade 3 severe infusion reactions, 2 (0.5%) patients with Grade 2 infusion reactions, 4 (1.0%) patients with Grade 1 infusion reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of infusion reactions was 0.76 months (range: 0.03 to 34.04 months). The median duration was 0.05 months (range: 0.03 to 0.53 months).<br><br>Serplulimab was temporarily discontinued in 0.3% (1/389) of patients due to infusion reactions. Infusion reactions resolved in 7 (1.8%) patients at the time of data cut-off.<br><br><u>Serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in non-squamous NSCLC</u><br><br>Infusion reactions were observed in 1.2% (6/503) of (95%CI: 0.4%-2.6%) patients with non-squamous NSCLC treated with serplulimab in combination with chemotherapy (carboplatin and pemetrexed) and/or HLX04 in pivotal study HLX10-002-NSCLC301. All patients experienced non-serious adverse events. There were 2 (0.4%) patients with Grade 2 infusion reactions, 4 (0.8%) patients with Grade 1 infusion reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of infusion reactions was 6.70 months (range: 0.16 to 17.84 months). The median duration was 0.03 months (range: 0.03 to 0.79 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in any patients due to infusion reactions. Infusion reactions resolved in 1 (0.2%) patient at the time of data cut-off.<br><br><u>Serplulimab in combination with cisplatin and 5-FU in OSCC</u><br><br>Infusion reactions were observed in 1.8% (7/382) (95%CI: 0.7%-3.7%) of patients with OSCC treated with serplulimab in combination with cisplatin and 5-FU in pivotal study HLX10-007-EC301. All patients experienced non-serious adverse events. There were 1 (0.3%) patient with Grade 3 severe infusion reactions, 3 (0.8%) patients with Grade 2 infusion reactions, and 3 (0.8%) patients with Grade 1 infusion reactions. There was no patient with a fatal outcome. |

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| | The median time to onset of infusion reactions was 1.81 months (range: 0.13 to 4.37 months). The median duration was 0.07 months (range: 0.03 to 1.74 months).<br><br>Serplulimab was not discontinued/temporarily discontinued in any patients due to infusion reactions. Infusion reactions resolved in 7 (1.8%) patients at the time of data cut-off.<br><br><u>Serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in squamous NSCLC</u><br><br>Infusion reactions were observed in 1.5% (7/455) (95%CI: 0.6%-3.1%) of patients with squamous NSCLC treated with serplulimab monotherapy or serplulimab in combination with carboplatin and nab-paclitaxel in pivotal study HLX10-004-NSCLC303. 0.7% (3/455) of patients experienced serious adverse events and 0.9% (4/455) of patients experienced non-serious adverse events. There were 1 (0.2%) patient with Grade 4 severe infusion reactions, 1 (0.2%) patient with Grade 3 severe infusion reactions, 4 (0.9%) patients with Grade 2 infusion reactions, and 1 (0.2%) patient with Grade 1 infusion reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of infusion reactions was 1.41 months (range: 0.72 to 21.29 months). The median duration was 0.03 months (range: 0.03 to 0.16 months).<br><br>Serplulimab was temporarily discontinued in 0.2% (1/455) of patients due to infusion reactions. Infusion reactions resolved in 7 (1.5%) patients at the time of data cut-off.<br><br><u>Serplulimab in pooled safety set</u><br><br>Across clinical studies, 1.7% (35/2086) (95%CI: 1.2%-2.3%) of patients developed infusion reactions. In the ≥RP2D/3D dose group (N=2 076), there were 3 patients who received serplulimab monotherapy, 25 patients who received serplulimab in combination with chemotherapy, and 7 patients who received serplulimab in combination with other monoclonal antibodies, experienced infusion reactions. Among the patients experiencing infusion reactions, 0.2% (5/2086) of patients experienced serious adverse events and 1.4% (30/2086) of patients experienced non-serious adverse events. There were 2 (<0.1%) patients with Grade 4 severe infusion reactions, 3 (0.1%) patients with Grade 3 severe infusion reactions, 15 (0.7%) patients with Grade 2 infusion reactions, 15 (0.7%) patients with Grade 1 infusion reactions. There was no patient with a fatal outcome.<br><br>The median time to onset of infusion reactions was 1.74 months (range: 0.03 to 34.04 months). The median duration was 0.07 months (range: 0.03 to 6.70 months). |

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| | Serplulimab was temporarily discontinued in <0.1% (2/2086) of patients due to infusion reactions. Infusion reactions resolved in 29 (1.4%) patients at the time of data cut-off.<br><br>Post-Marketing Data Sources<br><br>As of 21Mar2025, 38 infusion reaction events were collected from post-marketing origin. |
| Risk factors and risk groups: | No analysis of specific risk factors associated with severe infusion reactions has been performed. There are no known risk factors for patients treated with serplulimab developing severe infusion reactions. |
| Preventability: | 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. |
| Impact on the risk-benefit balance of the product: | Infusion reactions may be severe in individual patients. Serplulimab has shown to be effective in the following studies: Serplulimab combined with carboplatin and etoposide for the treatment of adult patients with ES-SCLC; Serplulimab combined with chemotherapy (carboplatin and pemetrexed) and/or HLX04 for the treatment of adult patients with non-squamous NSCLC; Serplulimab combined with cisplatin and 5-FU for the treatment of adult patients with OSCC; Serplulimab monotherapy or serplulimab combined with carboplatin and nab-paclitaxel in squamous NSCLC. Overall the benefit of serplulimab in combination with chemotherapy for treating a life-threatening condition is considered to outweigh the risk of severe infusion reactions that can be managed in clinical practice through monitoring to prevent serious complications.<br><br>The risk of severe infusion reactions will be further monitored and characterised in patients exposed to serplulimab in the ongoing clinical trials and during post-marketing activities. |
| Public health impact: | Serplulimab can be obtained only via prescription and will not be supposedly used outside the controlled environment. The warnings of drug adverse reactions and the recommended dose modifications for the adverse reactions are included in the SmPC. The potential impact on public health is considered to be low. |

**Important Potential Risks**

None.

### SVII.3.2. Presentation of the missing information

**Missing information:** Long-term safety in immunocompromised patients

Evidence source:

Not included in the clinical development programmes.

Population in need of further characterisation:

Further collection of data relating to the safety of serplulimab in immunocompromised patients will be evaluated in post-marketing activities.

# Part II: Module SVIII - Summary of the safety concerns

### Table SVIII.1: Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Immune-mediated adverse reactions<br>• Severe infusion reactions |
| Important potential risks | • None |
| Missing information | • Long-term safety in immunocompromised patients |

# Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

## III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

No routine pharmacovigilance activities are planned beyond adverse reactions reporting and signal detection.

## III.2. Additional pharmacovigilance activities

None.

## III.3. Summary table of additional Pharmacovigilance activities

Not applicable.

# Part IV: Plans for post-authorisation efficacy studies

Not applicable.

# Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

## Risk Minimisation Plan

## V.1. Routine risk minimisation measures

### Table Part V.1: Description of routine risk minimisation measures by safety concern

| Safety concern | Routine risk minimisation activities |
|---|---|
| Immune-mediated adverse reactions | Routine risk communication:<br>• Immune-mediated adverse reactions added in SmPC section 4.4.<br>• Immune-mediated adverse reactions listed as adverse reactions in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for withholding or permanently discontinuing serplulimab based on the severity of adverse reactions provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have inflammation provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription. |
| Severe infusion reactions | Routine risk communication:<br>• Description of the infusion-related reactions observed in clinical trials provided in SmPC section 4.4.<br>• Infusion-related reaction listed as adverse reaction in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: |

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| | • Guidance for withholding or discontinuing serplulimab based on the severity of the infusion-related reaction provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of infusion-related reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have infusion-related reactions provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription. |
| Long-term safety in immunocompromised patients | Routine risk communication:<br>• Information that patients with a history of active or prior documented autoimmune disease or active HIV infection, conditions requiring systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab were excluded from clinical trials provided in SmPC section 4.4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for the patient to check with their doctor before receiving serplulimab if they have an autoimmune disease in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription. |

## V.2. Additional risk minimisation measures

Educational Material (EM) including:

- Summary of Product Characteristics / Package Leaflet (will be voluntarily provided)
- Patient Card

Objectives:

Important risks covered by the EM:

- Immune-mediated adverse reactions
- Severe infusion reactions

The objective of the EM is to enhance the awareness of patients and/or their non-oncology caregivers on the signs and symptoms relevant to the early recognition/identification of those adverse events and to further increase awareness of physicians about immune-mediated adverse reactions and infusion-related reactions including their management.

Rationale for the additional risk minimisation activity:

In order to minimise the risks of immune-mediated adverse reactions and infusion-related reactions, EM are being distributed to relevant Healthcare Professionals (HCPs) and further to patients.

The EM 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. Details are included in **Annex 6**.

Target audience and planned distribution path:

The material will be distributed to relevant HCPs as a package and patients will receive their materials through the HCP.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness of the EMs is being measured via process and outcome indicators as follows:

*Process indicator*: Distribution metrics for the EM are being collected (confirmed distribution to and receipt by selected HCPs).

*Outcome indicator*: Analyses including qualitative descriptions and reporting rates of immune-mediated adverse reactions and infusion-related reactions as received from the post-marketing spontaneous reporting system will be conducted. A standard query will be added to the routine follow-up of spontaneously received adverse drug reactions, inquiring about the awareness of reporters of the EM. By obtaining this information, depending on obtained feedback, a comparison of spontaneous reporting rates and event patterns (event type, severity) between EM-aware vs unaware reporting sources might be possible.

**Removal of additional risk minimisation activities:**

Not applicable.

## V.3. Summary of risk minimisation measures

### Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Immune-mediated adverse reactions | **Routine risk minimisation measures:**<br>Routine risk communication:<br>• Immune-mediated adverse reactions added in SmPC section 4.4.<br>• Immune-mediated adverse reactions listed as adverse reactions in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for withholding or permanently discontinuing serplulimab based on the | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance** |

| | | |
|---|---|---|
| | severity of adverse reactions provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have inflammation provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>Patient Card | **activities:**<br>None |
| Severe infusion reactions | **Routine risk minimisation measures:**<br>Routine risk communication:<br>• Description of the infusion-related reactions observed in clinical trials provided in SmPC section 4.4.<br>• Infusion-related reaction listed as adverse reaction in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for withholding or discontinuing serplulimab based on the severity of the infusion-related reaction provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of infusion-related reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have infusion-related reactions provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>Patient Card | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |

| | | |
|---|---|---|
| Long-term safety in immunocompromised patients | **Routine risk minimisation measures:**<br>Routine risk communication:<br>• Information that patients with a history of active or prior documented autoimmune disease or active HIV infection, conditions requiring systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab were excluded from clinical trials provided in SmPC section 4.4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for the patient to check with their doctor before receiving serplulimab if they have an autoimmune disease in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |

# Part VI: Summary of the risk management plan

## Summary of risk management plan for HETRONIFLY (Serplulimab)

This is a summary of the risk management plan (RMP) for HETRONIFLY. The RMP details important risks of HETRONIFLY, how these risks can be minimised, and how more information will be obtained about HETRONIFLY's risks.

HETRONIFLY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how HETRONIFLY should be used.

This summary of the RMP for HETRONIFLY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of HETRONIFLY's RMP.

## I. The medicine and what it is used for

HETRONIFLY is authorised for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), non-squamous non-small cell lung carcinoma (NSCLC), oesophageal squamous cell carcinoma (OSCC) and squamous NSCLC (see SmPC for the full indication). It contains serplulimab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of HETRONIFLY’s benefits can be found in HETRONIFLY’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of HETRONIFLY, together with measures to minimise such risks and the proposed studies for learning more about HETRONIFLY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In the case of HETRONIFLY, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR (Periodic Safety Update Report) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of HETRONIFLY is not yet available, it is listed under 'missing information' below.

## *II.A List of important risks and missing information*

Important risks of HETRONIFLY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of HETRONIFLY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | • Immune-mediated adverse reactions<br>• Severe infusion reactions |
| Important potential risks | • None |
| Missing information | • Long-term safety in immunocompromised patients |

## *II.B Summary of important risks*

| **Important Identified Risk:** Immune-mediated adverse reactions | |
|---|---|
| Evidence for linking the risk to the medicine | The safety of serplulimab was evaluated in the clinical trials with serplulimab single agent and in the clinical trials with combined administration. Immune-mediated adverse reactions (including: immune-mediated myocarditis; immune-mediated pancreatitis; immune-mediated lung disease; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis and renal dysfunction; immune-mediated endocrinopathies; immune-mediated skin adverse reactions; immune-mediated uveitis; other immune-mediated adverse reactions) were observed in patients treated with serplulimab in these clinical trials. |
| Risk factors and risk groups | No analysis of specific risk factors associated with immune-mediated adverse reactions has been performed. There are no known risk factors for patients treated with serplulimab developing the important identified risk. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>Routine risk communication: |

| | |
|---|---|
| | • Immune-mediated adverse reactions added in SmPC section 4.4.<br>• Immune-mediated adverse reactions listed as adverse reactions in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for withholding or permanently discontinuing serplulimab based on the severity of adverse reactions provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have inflammation provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>Patient Card |

| **Important Identified Risk:** Severe infusion reactions | |
|---|---|
| Evidence for linking the risk to the medicine | The safety of serplulimab was evaluated in the clinical trials with serplulimab single agent and in the clinical trials with combined administration. Severe infusion reactions were observed in patients treated with serplulimab in these clinical trials. |
| Risk factors and risk groups | No analysis of specific risk factors associated with severe infusion reactions has been performed. There are no known risk factors for patients treated with serplulimab developing severe infusion reactions. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>Routine risk communication:<br>• Description of the infusion-related reactions observed in clinical trials provided in SmPC section 4.4.<br>• Infusion-related reaction listed as adverse reaction in SmPC section 4.8.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: |

| | |
|---|---|
| | • Guidance for withholding or discontinuing serplulimab based on the severity of the infusion-related reaction provided in SmPC section 4.2.<br>• Warning to monitor for signs and symptoms of infusion-related reactions and treatment advice based on severity included in SmPC section 4.4.<br>• Warning for the patient to talk to their doctor if they have infusion-related reactions provided in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>Patient Card |

| **Missing Information:** Long-term safety in immunocompromised patients | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>Routine risk communication:<br>• Information that patients with a history of active or prior documented autoimmune disease or active HIV infection, conditions requiring systemic immunosuppressive medicinal products within 2 weeks prior to receiving serplulimab were excluded from clinical trials provided in SmPC section 4.4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Guidance for the patient to check with their doctor before receiving serplulimab if they have an autoimmune disease in Package leaflet.<br>Other routine risk minimisation measures:<br>• Legal status: subject to restricted medical prescription.<br>**Additional risk minimisation measures:**<br>None |

## *II.C Post-authorisation development plan*

## II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of HETRONIFLY.

## II.C.2. Other studies in post-authorisation development plan

Not applicable.

# Part VII: Annexes

## *Annex 1 – EudraVigilance Interface*

Not applicable.

## *Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme*

None.

## *Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan*

Not applicable.

## *Annex 4 - Specific adverse drug reaction follow-up forms*

Not Applicable.

## *Annex 5 - Protocols for proposed and ongoing studies in RMP part IV*

Not Applicable.

## *Annex 6 - Details of proposed additional risk minimisation activities*

Draft key messages of the additional risk minimisation measures

In order to manage the risks, the MAH has developed educational materials which will be distributed to relevant HCPs and further to patients.

**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 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.

**Evaluation of effectiveness of additional risk minimisation measures:**

Effectiveness of the EMs is being measured via process and outcome indicators as follows:

*Process indicator*: Distribution metrics for the EM are being collected (confirmed distribution to and receipt by selected HCPs).

*Outcome indicator*: Analyses including qualitative descriptions and reporting rates of immune-mediated adverse reactions and infusion-related reactions as received from the post-marketing spontaneous reporting system will be conducted. A standard query will be added to the routine follow-up of spontaneously received adverse drug reactions, inquiring about the awareness of reporters of the EM. By obtaining this information, depending on obtained feedback, a comparison of spontaneous reporting rates and event patterns (event type, severity) between EM-aware vs unaware reporting sources might be possible.

**The Patient Card is shown as follows:**

# **HETRONIFLY** (Serplulimab) **Patient Card**

**IMPORTANT** – This card contains important safety information on your serplulimab treatment. **Keep this card with you at all times** during your treatment and at least 3 months after completing your treatment with serplulimab. Always show it to any healthcare professional involved in your treatment.

Important Safety Information to minimise the risk of immune-mediated side effects.

- Contact your specialist right away if you develop any signs or symptoms described in this card.
- For further information, consult the Patient Information Leaflet or call Accord Medical Information on Tel: +{Telephone number}.

*Contact your specialist right away if you develop any signs or symptoms, which may include those listed below:*

| | | |
|---|---|---|
| Lungs<br>l Breathing difficulties<br>l Cough<br>Liver<br>l Yellowing of skin and whites of your eyes (jaundice)<br>l Severe nausea or vomiting<br>l Pain on the right side of your stomach area (abdomen)<br>l Drowsiness<br>l Dark urine (tea coloured)<br>l Bleeding or bruising more easily than normal<br>l Feeling less hungry than usual<br>l Tiredness<br>l Abnormal liver function tests<br>Heart<br>l Trouble breathing<br>l Dizziness or fainting<br>l Fever<br>l Chest pain and chest tightness<br>l Flu-like symptoms<br>Hormone glands<br>l Extreme tiredness<br>l Rapid heart beat<br>l Increased sweating<br>l Changes in mood or behaviour, such as irritability or forgetfulness<br>l Feeling cold<br>l Very low blood pressure (fainting, dizziness, fatigue, nausea)<br>l Weight change<br>l Headache | Diabetes / diabetic ketoacidosis<br>l Feeling more hungry or thirsty than usual<br>l Needing to urinate more often<br>l Weight loss<br>l Feeling tired<br>l Having difficulty thinking clearly<br>l Breath that smells sweet or fruity<br>l Feeling sick or being sick<br>l Stomach pain<br>l Deep or fast breathing<br>Bowel and stomach<br>l Diarrhoea (loose stools)<br>l More bowel movements than usual<br>l Blood in your stools or dark, tarry, sticky stools<br>l Severe stomach (abdomen) pain or tenderness<br>Kidneys<br>l Abnormal kidney function tests<br>l Urinating less than usual<br>l Blood in your urine<br>l Swelling in your ankles<br>Eye<br>l Eye pain<br>l Eye redness<br>l Sensitivity to light<br>l Blurred or cloudy vision<br>l Small shapes moving across your field of vision (floaters)<br>l Loss of peripheral vision (the ability to see objects at the side of your field of vision) | Pancreas<br>l Abdominal pain<br>l Nausea<br>l Vomiting<br>Muscle<br>l Muscle pain<br>l Weakness<br>Skin<br>l Rash or itching<br>l Skin blistering<br>l Ulcers in mouth or other mucous membrane<br>Nervous system<br>l Headache or stiff neck<br>l Fever<br>l Feeling tired or weak<br>l Chills<br>l Vomiting<br>l Confusion<br>l Memory problems or feeling sleepy<br>l Fits (seizures)<br>l Seeing or hearing things that are not really there (hallucinations)<br>Infusion-related reactions<br>l Shortness of breath or wheezing<br>l Chills or shaking<br>l Bumpy rash or skin wheals<br>l Flushing<br>l Low blood pressure (dizziness, fatigue, nausea)<br>l Fever<br>l Back pain<br>l Abdominal pain |

IMPORTANT

- Do not attempt to diagnose or treat side effects by yourself.
- Carry this Patient Card with you at all times, especially when you travel, whenever you go to the Emergency Room, or when you must see another doctor, nurse or pharmacist.
- Be sure to notify any healthcare professional you see that you are being treated with serplulimab and show them this card.

IMPORTANT INFORMATION FOR HEALTH CARE PROVIDERS

| | |
|---|---|
| This patient is being treated with Hetronifly (serplulimab), which can cause infusion-related reactions as well as immune-mediated adverse reactions that affect the lungs, liver, heart, intestines, hormone glands, kidneys, pancreas and other organs. Early diagnosis and appropriate management are essential to minimise any consequences of immune-mediated adverse reactions.<br>For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes.<br>Specific guidelines for managing immune-mediated adverse reactions and infusion-related reactions are available in the Summary of Product Characteristics for serplulimab available at *www.ema.europa.eu* or call Accord Medical Information on Tel: +{Telephone number} for more information. | *Assess patients for signs and symptoms of pneumonitis, hepatitis, myocarditis, colitis, endocrinopathies (including hypothyroidism, hyperthyroidism, thyroiditis, adrenal gland disorders, pituitary disorders, diabetes mellitus/hyperglycaemia), pancreatitis, nephritis and renal dysfunction, uveitis, and other immune-mediated adverse reactions, including myasthenia gravis and myasthenic syndrome, reported in patients receiving serplulimab.* |

Please consult the Summary of Product Characteristics and Patient Information Leaflet (PIL) for serplulimab at *www.ema.europa.eu* or call Accord Medical Information on Tel: +{Telephone number} for more information.

IMPORTANT CONTACT INFORMATION

Name of Specialist _____
Phone _____
After-hours Phone _____
My Name _____
My Phone _____
Emergency Contact (Name) _____
Emergency Contact (Phone) _____

## *Annex 7 - Other supporting data (including referenced material)*

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## *Annex 8 - Summary of changes to the risk management plan over time*

| Version | Approval date | Change |
|---|---|---|
| 1.0 | 19Sep2024 | • New version |
| 2.0 | 26Mar2026 | • Added proposed indication of non-squamous NSCLC and OSCC in Part I.<br>• Added epidemiology of non-squamous NSCLC and OSCC in Part II: Module SI.<br>• Updated the status and cut-off date of pooled studies in Part II: Module SIII.<br>• Updated the exclusion criteria in pivotal studies in Part II: Module SIV.<br>• Updated the method used to calculate exposure and post-marketing data in Part II: Module SV.<br>• Updated the risks not considered important in Part II: Module SVII.1.<br>• Updated safety data of pooled studies in Part II: Module SVII.1 and Part II: Module SVII.3.<br>• Updated safety data of pivotal study for ES-SCLC and post-marketing data in Part II: Module SVII.3.<br>• Added safety data of pivotal study for non-squamous NSCLC and OSCC in Part II: Module SVII.3.<br>• Patient Card in Annex 6 updated to instruct HCPs to also look out for signs and symptoms of myasthenia gravis and myasthenic syndromes. |
| 3.0 | At the time of authorisation | • Added proposed indication of squamous NSCLC in Part I.<br>• Added epidemiology of squamous NSCLC in Part II: Module SI.<br>• Added exposure data of pivotal study for squamous NSCLC in the Part II: Module SIII.<br>• Added safety data of pivotal study for squamous NSCLC in Part II: Module SVII.3. |

# Serplulimab (HLX10) Core RMP V30_EMA_Clean_Based on V20 Clean_Consolidated RMP (nsqNSCLC ESCC sqNSCLC)_20260506

## Document information

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