swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ZYNYZ

International non-proprietary name: retifanlimab

Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	500 mg/20 mL
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Incyte Biosciences International
Marketing authorisation no.:	70012
Decision and decision date:	approved on 24 June 2025

Note:

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

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

Table of contents

1 Terms, definitions, abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CDRs	Complementarity determining regions
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCC	Merkel cell carcinoma
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PD-1	Programmed death receptor-1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event

SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
WCB	Working cell bank

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

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

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

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 13 January 2025.

2.2 Indication and dosage

2.2.1 Requested indication

ZYNYZ is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

2.2.2 Approved indication

ZYNYZ is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The proposed dosing regimen for ZYNYZ is 500 mg administered intravenously every 4 weeks over 30 minutes. Treatment should continue until disease progression or unacceptable toxicity, and for a maximum 2 years.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	22 November 2024
Formal control completed	26 November 2024
List of Questions (LoQ)	30 January 2025

Response to LoQ	20 March 2025
Preliminary decision	9 May 2025
Response to preliminary decision	4 June 2025
Final decision	24 June 2025
Decision	approval

3 Quality aspects

3.1 Drug substance

INN: relifanlimab
Molecular mass: approx. 148 kDa
Molecular structure:
Retifanlimab is a humanised hinge-stabilised IgG4, IgK monoclonal antibody that recognises human PD-1 expressed by T and B cells. It has a serine to proline mutation in the human heavy chain CH_2 region to greatly reduce or eliminate inter-chain disulfide instability of the hinge region. Moreover, a single point mutation was introduced into the variable region of the light chain to remove an N-linked glycosylation site in CDR1. Finally, the C-terminal lysine has been eliminated from the retifanlimab heavy chain DNA sequence to eliminate lysine truncation as one of the post-translational modifications. The light chain and the heavy chain consist of 218 and 445 amino acids, respectively.

Manufacture:
Retifanlimab is produced in a recombinant Chinese hamster ovary cell line. A two-tiered cell banking system of master cell bank and working cell bank (WCB) is in place. A single working cell bank (WCB) vial is thawed and expanded before inoculation into a production bioreactor. The unprocessed bulk containing retifanlimab is clarified. The resulting harvested cell culture fluid is stored until the start of the purification process, which includes a series of chromatography, viral inactivation and filtration steps. The cell culture and purification processes for retifanlimab drug substance were both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.
Some changes, including production scale, were implemented during development of the manufacturing process for the drug substance. However, comparability studies, including batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the manufacturing processes.
Characterisation of the physicochemical and biological properties of the retifanlimab drug substance and its impurities was performed using state-of-the-art methods.

Specification:
The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, clinical experience, batch analysis, and stability data, and are in conformance with current compendial or regulatory guidelines.
The batch analysis data comply with the drug substance specifications. All specific analytical methods are validated.

Stability:
No significant changes were observed during storage of retifanlimab drug substance under the proposed storage conditions.

3.2 Drug product

Description and composition:
The drug product is a sterile, preservative-free concentrate for solution for intravenous infusion. The product is a clear to slightly opalescent, colourless to pale yellow solution. It is supplied as a single-dose presentation with 500 mg retifanlimab per vial and 20 mL solution per vial (25 mg/mL).

Pharmaceutical development:
The formulation of the drug substance and drug product is identical. The intended commercial formulation is the same as that used in clinical studies. All excipients (sodium acetate trihydrate, glacial acetic acid, sucrose, polysorbate 80, and water for injection) are of compendial grade and commonly used for the formulation of biopharmaceuticals.
Several drug product dosage strengths and filling facilities were used during clinical development. However, comparability studies, which included batch release data and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.
Compatibility studies were conducted to establish the in-use stability of diluted drug product with the intended materials and conditions of use.

Manufacture:
The drug product manufacturing process comprises thawing of drug substance, pooling and mixing, bioburden reduction filtration, sterile filtration and filling in vials, stoppering and capping, and visual inspection, followed by storage at 2 - 8°C until packaging and labelling.
The drug product manufacturing process was validated using several consecutive batches and the data demonstrated consistent production.

Specification:
The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.
Batch analysis data comply with the drug product specifications. All specific analytical methods are validated.

Container closure system:
The primary packaging is a single-use 20 mL type I glass vial closed with a chlorobutyl rubber stopper, an aluminium seal, and plastic overseal. The materials used for the type I glass syringe barrel and the plunger stopper meet compendial requirements.

Stability:
A shelf life of 24 months was granted for the drug product stored at 5 ± 3°C, protected from light.

3.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated. Safety of the product regarding viral and non-viral contaminants was adequately addressed.

4 Nonclinical aspects

4.1 Nonclinical conclusions

The Nonclinical Assessment Division conducted an abridged evaluation of the marketing authorisation application for Zynyz, which was based on EPAR assessment report EMA/49916/2024, dated 22 February 2024 and provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Zynyz in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals. From the nonclinical standpoint, there is no objection against approval.

5 Clinical aspects

5.1 Final clinical benefit risk assessment

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authorities EMA (Procedure No. EMEA/H/C/006194/0000) and FDA (Application No. 761334Orig1s000).

6 Risk management plan summary

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

7 Appendix

Approved Information for healthcare professionals

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

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

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

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

ZYNYZ

Composition

Active substances

Retifanlimab (a monoclonal humanised immunoglobulin G4 (IgG4) directed towards the ligand of the programmed cell death protein 1 (PD-1) of ovarian Chinese hamster cells grown in suspension using the recombinant DNA technique).

Excipients

Sodium acetate trihydrate (for pH adjustment) (E262); Acetic acid (E260); Sucrose; Polysorbate 80 (E433); Water for injection
Each vial of 20 mL contains less than 23 mg sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile concentrate). Clear to slightly opalescent, colourless to pale yellow solution, with a pH of 5.1 and osmolality between 275 and 355 mOsm/kg.
Each mL of concentrate contains 25 mg of retifanlimab. One vial of 20 mL concentrate contains 500 mg of retifanlimab.

Indications/Uses

ZYNYZ is indicated as monotherapy for the first line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

Dosage/Administration

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

Usual dosage

Adults
The recommended dose is 500 mg retifanlimab every 4 weeks administered as an intravenous infusion over 30 minutes.

Treatment duration

Treatment should continue until disease progression or unacceptable toxicity for up to 2 years.

Dose modifications

Dose escalation or reduction of retifanlimab is not indicated.

Recommended dose modifications to manage immune-related adverse reactions are provided in Table 1 (see also sections “Warnings and precautions” and “Undesirable effects”).

Table 1: Recommended dose modifications

Adverse reaction	Severity[a]	Dose modification
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1.
	Grades 3 or 4	Permanently discontinue.
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1.
	Recurrent Grade 3 or Grade 4	Permanently discontinue.
Hepatitis with no tumour involvement of the liver OR Increased total bilirubin	Grade 3 with AST or ALT greater than 3 but no more than 8 times ULN OR TB increases to more than 1.5 and up to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.
	Grade 4 with AST or ALT increases to more than 8 times ULN OR TB greater than 3 times ULN	Permanently discontinue.
Hepatitis with tumour involvement of the liver OR Increased total bilirubin	Grade 3 with AST or ALT more than 5 and up to 10 times ULN OR TB greater than 1.5 but no more than 3 times ULN	Withhold until adverse reactions recover to Grades 0-1. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.
	Grade 4 with AST or ALT increase to more than 10 times ULN OR TB greater than 3 times ULN	Permanently discontinue.

Adverse reaction	Severity[a]	Dose modification
Endocrinopathies • Adrenal insufficiency • Hypothyroidism • Hyperthyroidism • Type 1 diabetes mellitus • Hyperglycaemia • Hypophysitis	Grade 2 adrenal insufficiency	Withhold until adverse reactions recover to Grades 0-1 or otherwise clinically stable.
	Grades 3 or 4 adrenal insufficiency	Withhold until adverse reactions recover to Grades 0-1. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.
	Grades 3 or 4 hypothyroidism	Withhold until adverse reactions recover to Grades 0-1 or is otherwise clinically stable.
	Grades 3 or 4 hyperthyroidism	Withhold until adverse reactions recover to Grades 0-1 or is otherwise clinically stable.
	Grades 3 or 4 type 1 diabetes mellitus (or hyperglycaemia)	Withhold until adverse reactions recover to Grades 0-1 or is otherwise clinically stable.
	Grade 2 hypophysitis (asymptomatic)	Withhold until adverse reactions recover to Grades 0-1. May restart after controlled by hormone replacement therapy.
	Grade 2 hypophysitis (symptomatic e.g., headaches, visual disturbances)	Withhold until adverse reactions recover to Grades 0-1. May restart after controlled by hormone replacement therapy, if indicated and steroid taper is complete.
	Grade 3 or 4 hypophysitis (symptomatic)	Withhold until adverse reactions recover to Grades 0-1. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.

Adverse reaction	Severity[a]	Dose modification
Nephritis with renal dysfunction	Grade 2 increased blood creatinine	Withhold until adverse reactions recover to Grades 0-1.
	Grade 3 or 4 increased blood creatinine	Permanently discontinue.[b]
Skin reactions	Grade 3 or suspected SJS or suspected TEN Persistent Grade 2 (≥ 2 weeks)	Withhold until adverse reactions recover to Grades 0-1.
	Grade 4 or confirmed SJS or confirmed TEN	Permanently discontinue.
Myocarditis	Confirmed Grades 2, 3 or 4	Permanently discontinue.
Other immune-related adverse reactions (including myositis, encephalitis, demyelinating neuropathy, Guillain Barré syndrome, sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, uveitis, diabetic ketoacidosis, arthralgia)	Grade 3	Withhold until adverse reactions recover to Grades 0-1.
	Grade 4	Permanently discontinue.
Persistent Grade 2 or 3 immune-related adverse reactions (excluding endocrinopathies)	Grade 2 or 3 (≥ 12 weeks after last dose) Recurrent Grade 3 or 4 Recurrent Grade 2 pneumonitis	Permanently discontinue.
Infusion-related reactions	Grade 1	Interrupt or slow the rate of infusion.
	Grade 2	First occurrence: Interrupt infusion and resume at 50% of the original rate if symptoms resolve within 1 hour. Subsequent occurrences: Permanently discontinue after recommended prophylaxis.
	Grade 3	Permanently discontinue. If rapidly responsive to symptomatic management and/or to brief interruption of infusion, retifanlimab does

Adverse reaction	Severity[a]	Dose modification
		not need to be permanently discontinued.
	Grade 4	Permanently discontinue.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; TB = total bilirubin; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

[a] Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

[b] Permanently discontinue only if retifanlimab is directly implicated in renal toxicity.

Elderly patients

No dose adjustment is needed for patients who are aged 65 years or over (see section “Pharmacokinetics”).

Patients with renal disorders

No dose adjustment is needed for patients with mild or moderate renal impairment. There is insufficient data in patients with severe renal impairment (creatinine clearance < 30 mL/min) and no data for patients with end-stage renal disease and therefore no dosing recommendation can be made (see section “Pharmacokinetics”).

Patients with hepatic disorders

No dose adjustment is needed for patients with mild hepatic impairment. There are insufficient data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment and therefore no dosing recommendations can be made (see section “Pharmacokinetics”).

Paediatric population

ZYNYZ is not indicated in children and adolescents below the age of 18 years.

Mode of administration

ZYNYZ is for intravenous use. It must be administered by intravenous infusion over 30 minutes.
ZYNYZ must not be administered as an intravenous push or bolus injection.
ZYNYZ can only be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone, polyvinylidene fluoride, or cellulose acetate 0.2 micron to 5 micron in-line or add-on filter or 15 micron mesh in-line or add-on filter. Other medicinal products should not be co-administered through the same infusion line.

Contraindications

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

Warnings and precautions

Immune-related adverse reactions

Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with retifanlimab. Immune-related adverse reactions can occur in any organ or tissue and may affect more than one body system simultaneously. While immune-related adverse reactions usually occur during treatment, symptoms can also manifest after discontinuation. Important immune-related adverse reactions listed in this section are not inclusive of all possible immune-related reactions.

Early identification and management of immune-related adverse reactions is essential to ensure safe use of retifanlimab. Patients should be monitored for symptoms and signs of immune-related adverse reactions. Blood chemistries, including liver tests and thyroid function tests, should be evaluated at start of treatment and periodically during treatment. For suspected immune-related adverse reactions, adequate evaluation including specialty consultation should be ensured to confirm aetiology or exclude other causes.

Based on the severity of the adverse reaction, treatment with retifanlimab should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued for at least 1 month (see Table 1).

Immune-related pneumonitis

Immune-related pneumonitis has been reported in patients receiving retifanlimab (see section ”Undesirable effects”). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with retifanlimab treatment modifications and corticosteroids (see Table 1).

Immune-related colitis

Immune-related colitis has been reported in patients receiving retifanlimab (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of colitis and managed with retifanlimab treatment modifications, anti-diarrhoeal agents and corticosteroids (see Table 1).

Immune-related hepatitis

Immune-related hepatitis has been reported in patients receiving retifanlimab (see section “Undesirable effects”). Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with retifanlimab treatment modifications and corticosteroids (see Table 1). For Grade 1 hepatitis, liver chemistry monitoring should be increased to twice per week until liver chemistry tests return to baseline.

Immune-related endocrinopathies

Immune-related endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and diabetic ketoacidosis have been reported in patients receiving retifanlimab (see section “Undesirable effects”). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and for cortisol, as indicated based on symptoms and/or falling thyroid-stimulating hormone).

Hypothyroidism and hyperthyroidism
Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) have been reported in patients receiving retifanlimab. Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) should be managed with retifanlimab treatment modifications as recommended in Table 1.

Hypophysitis
Immune related hypophysitis has been observed in patients receiving retifanlimab (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of hypophysitis and managed with retifanlimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated (see Table 1).

Adrenal insufficiency
Immune-related adrenal insufficiency has been reported in patients receiving retifanlimab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency and managed with corticosteroids and hormone replacement, as clinically indicated (see Table 1).

Type 1 Diabetes mellitus
Immune-related type 1 diabetes mellitus has been observed in patients treated with PD-1 inhibitors (see section “Undesirable effects”). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and retifanlimab treatment modifications (see Table 1).

Immune-related nephritis
Immune-related nephritis has been reported in patients receiving retifanlimab (see section “Undesirable effects”). Patients should be monitored for changes in renal function and managed with retifanlimab treatment modifications and corticosteroids (see section “Dosage/Administration”).

Immune-related skin reactions
Immune-related skin reactions, such as toxic epidermal necrolysis, have been reported in patients receiving retifanlimab (see section “Undesirable effects”). Events of Stevens-Johnson syndrome have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of skin reactions. Immune-related skin reactions should be managed as recommended in Table 1.

Caution should be used when considering the use of retifanlimab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other checkpoint inhibitors.

Other immune-related adverse reactions

The following clinically significant immune-related adverse events, including serious or fatal cases, occurred at an incidence of <1% in 653 patients who received ZYNYZ (see Adverse Reactions), or have been reported with the use of other PD-1/PD-L1 blocking antibodies:

Cardiac/vascular: myocarditis, pericarditis, vasculitis

Gastrointestinal: pancreatitis, including increased serum levels of amylase and lipase, gastritis, duodenitis, coeliac disease, exocrine pancreatic impairment.

Hepatobiliary: cholangitis

Musculoskeletal: myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica, eosinophilic fasciitis

Neurological: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, polyneuropathy, radiculopathy, vocal cord paralysis

Ocular: uveitis, iritis, keratitis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Endocrine: hypoparathyroidism

Other (Hematologic/Immune): hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with retifanlimab treatment modifications as described in section “Dosage/Administration”.

Patients suffering from a pre-existing autoimmune disease
Patients suffering from a pre-existing autoimmune disease (AID) were excluded from clinical trials assessing retifanlimab. Data from observational studies of immune checkpoint inhibitors indicate an

increased risk of immune-related adverse events in patients with AID compared to patients without pre-existing AID. In addition, although flare-ups of the underlying AID were frequently observed, they were mostly mild and easy to treat.

Infusion-related reactions

As with any therapeutic protein, retifanlimab can cause infusion-related reactions, some of which may be severe. Patients should be monitored for signs and symptoms of infusion-related reactions. Retifanlimab treatment should be interrupted or the rate of infusion slowed or treatment should be permanently discontinued based on severity of reaction and the response to treatment (see section “Dosage/Administration”). Premedication with an antipyretic and/or an antihistamine should be considered for patients who have had previous clinically significant reactions to infusions of therapeutic proteins (see section “Undesirable effects”).

Transplant-related adverse reactions

Solid organ transplant rejection

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with retifanlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with retifanlimab versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GvHD), acute GvHD, chronic GvHD, hepatic veno-occlusive disease after reduced intensity conditioning and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Patients should be closely followed for evidence of transplant-related complications and prompt intervention may be required. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

Patients excluded from the clinical programme

Patients with the following status were excluded from the clinical programme: Eastern Cooperative Oncology Group (ECOG) baseline performance score ≥ 2; symptomatic central nervous system metastases; prior immunotherapy or autoimmune disease that required systemic therapy with immunosuppressant agents; history of other malignancies within the last 3 years; organ transplant; or

active hepatitis infection. Patients with uncontrolled HIV infection (CD4+ count < 300 cells/µL, detectable viral load, or not receiving highly active antiretroviral therapy) were also excluded.

Excipients with known effect

Sodium

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

Interactions

No formal pharmacokinetic drug interaction studies have been conducted with retifanlimab. Since retifanlimab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting retifanlimab, except for physiological doses of systemic corticosteroids (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of retifanlimab. However, systemic corticosteroids or other immunosuppressants can be used after starting retifanlimab to treat immune-related adverse reactions (see sections “Dosage/Administration” and “Warnings and precautions”).

Retifanlimab is not expected to be a victim or perpetrator of drug-drug interactions involving drug transporters or CYP enzymes.

Pregnancy, lactation

Pregnancy

There are no data from the use of retifanlimab in pregnant women. Animal reproduction studies have not been conducted with retifanlimab. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death. Therefore, based on its mechanism of action, retifanlimab can cause foetal harm when administered to a pregnant woman. Human IgG4 immunoglobulins are known to cross the placenta; therefore, retifanlimab has the potential to be transmitted from the mother to the developing foetus. ZYNYZ is not recommended during pregnancy and in women of childbearing potential not using effective contraception (see section “Preclinical data”).

Lactation

It is unknown whether retifanlimab is excreted in human milk. There is insufficient information on the excretion of retifanlimab in animal milk.
Human IgGs are known to be excreted in breast milk; consequently, a risk to the breast-fed infant cannot be excluded. Because of the risk of serious adverse events in breast-fed children, women are advised not to breastfeed during the treatment and for 4 months after the last dose of ZYNYZ.

Fertility

No clinical data are available on the possible effects of retifanlimab on fertility. Animal reproduction studies to evaluate the effect of retifanlimab on fertility have not been conducted.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

Immune-related adverse reactions occurred with retifanlimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of retifanlimab (see “Description of selected adverse reactions” below).

The most common adverse reactions are fatigue (32.8%), rash (17%), diarrhoea (16.8%), anaemia (15.9%), pruritus (13.8%), arthralgia (11.6%), constipation (11.6%), nausea (13.8%), pyrexia (12.3%) and decreased appetite (11.3%). Adverse reactions were serious in 11% of patients; most serious adverse reactions were immune-related adverse reactions.

ZYNYZ was permanently discontinued due to adverse reactions in 6.7% of patients; most of them were immune-related events.

List of adverse reactions

The safety profile of retifanlimab is based on pooled data from 653 patients with advanced solid malignancies who received at least 1 dose of retifanlimab as monotherapy, including 107 patients with metastatic or recurrent locally advanced MCC. Median duration of treatment was 3.7 months (range, 1 day – 28.6 months). The frequencies included below are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Adverse reactions are listed below by system organ class and frequency. The frequency categories are defined as follows:

"very common" (≥1/10),

"common" (≥1/100 to <1/10),

“uncommon” (≥1/1000 to <1/100),

“rare” (≥1/10,000 to <1/1000),

“very rare” (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing incidence.

Table 2: Adverse reactions in patients treated with retifanlimab (N = 653)

System organ class	Frequency of all grades	Frequency of grades 3-4
Blood and lymphatic system disorders	**Very common** Anaemia[a]	**Common** Anaemia[a]
Endocrine disorders	**Common** Hypothyroidism, Hyperthyroidism **Uncommon** Adrenal insufficiency Thyroiditis[b] Hypophysitis Type 1 diabetes mellitus[c]	**Uncommon** Adrenal insufficiency Hypophysitis Type 1 diabetes mellitus[c]
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Common** Paraesthesia **Uncommon** Polyneuropathy[d] Radiculopathy Vocal cord paralysis	**Uncommon** Polyneuropathy[d] Radiculopathy
Eye disorders	**Uncommon** Uveitis[e] Keratitis	**Uncommon** Uveitis[e]
Cardiac disorders	**Uncommon** Pericarditis Myocarditis	**Uncommon** Myocarditis
Respiratory, thoracic and mediastinal disorders	**Common** Pneumonitis[f]	**Uncommon** Pneumonitis[f]
Gastrointestinal disorders	**Very common** Diarrhoea Nausea Constipation **Common** Colitis[g] **Uncommon** Pancreatitis	**Uncommon** Diarrhoea Pancreatitis Colitis[g]
Hepatobiliary disorders	**Common** Hepatitis[h]	**Uncommon** Hepatitis[h]

System organ class	Frequency of all grades	Frequency of grades 3-4
	Uncommon Hepatocellular injury Hyperbilirubinaemia Cholangitis	Hepatocellular injury Cholangitis Hyperbilirubinaemia
Skin and subcutaneous skin disorders	**Very common** Rash[i] Pruritus	**Common** Rash[i]
Musculoskeletal and connective tissue disorders	**Very common** Arthralgia **Uncommon** Arthritis[j] Myositis Eosinophilic fasciitis Polymyalgia rheumatica	**Uncommon** Arthralgia Arthritis[j] Myositis Eosinophilic fasciitis
Renal and urinary disorders	**Common** Acute kidney injury **Uncommon** Renal failure Tubulointerstitial nephritis	**Uncommon** Acute kidney injury Tubulointerstitial nephritis
General disorders and administration site conditions	**Very common** Fatigue[k] Pyrexia	**Common** Fatigue[k] **Uncommon** Pyrexia
Investigations	**Common** Transaminases increased[l] Blood creatinine increased Amylase increased Lipase increased Blood bilirubin increased Blood thyroid stimulating hormone increased **Uncommon** Blood thyroid stimulating hormone decreased	**Common** Transaminases increased[l] Blood bilirubin increased Amylase increased Lipase increased **Uncommon** Blood creatinine increased
Injury, poisoning and procedural complications	**Common** Infusion-related reaction[m]	**Uncommon** Infusion-related reaction[m]

[a] Includes anaemia, iron deficiency anaemia, anaemia of malignant disease and anaemia vitamin B12 deficiency
[b] Includes thyroiditis and autoimmune thyroiditis
[c] Includes diabetic ketoacidosis
[d] Includes polyneuropathy and demyelinating polyneuropathy
[e] Includes uveitis and iritis
[f] Includes pneumonitis, interstitial lung disease, organising pneumonia and lung infiltration
[g] Includes colitis and immune-mediated enterocolitis
[h] Includes hepatitis and autoimmune hepatitis
[i] Includes rash, rash maculo-papular, rash erythematous, rash pruritic, dermatitis, psoriasis, rash macular, rash papular, lichenoid keratosis, rash pustular, dermatitis bullous, palmar-plantar erythrodyseasthesia syndrome, toxic epidermal necrolysis and toxic skin eruption
[j] Includes arthritis and polyarthritis
[k] Includes asthenia and fatigue
[l] Includes transaminases increased, alanine aminotransferase increased and aspartate

System organ class	Frequency of all grades	Frequency of grades 3-4

aminotransferase increased

[m] Includes drug hypersensitivity and infusion-related reaction

Description of selected adverse reactions

The selected adverse reactions described below are based on the safety of retifanlimab in a pooled safety population of 653 patients with advanced solid malignancies, including patients with metastatic or recurrent locally advanced MCC. The management guidelines for these adverse reactions are described in section “Dosage/Administration”.

Immune-related adverse reactions (see section “Warnings and precautions”)

Immune-related pneumonitis

Immune-related pneumonitis occurred in 2.5% of patients receiving retifanlimab, including 0.9% of patients with Grade 2, 0.9% of patients with Grade 3 and 0.2% of patients with Grade 5. The median time to onset of pneumonitis was 126 days (range, 43 – 673 days). Pneumonitis led to discontinuation of retifanlimab in 0.3% of patients. Among the patients with pneumonitis, 75% received systemic corticosteroids and 6.3% received another immunosuppressant (infliximab). Pneumonitis resolved in 81.3% of patients, with a median time to resolution of 39 days (range, 9 – 213 days).

Immune-related colitis

Immune-related colitis occurred in 3.1% of patients receiving retifanlimab, including 1.2% of patients with Grade 2, 0.8% of patients with Grade 3 and 0.3% of patients with Grade 4. The median time to onset of colitis was 79 days (range, 2 – 749 days). Colitis led to discontinuation of retifanlimab in 1.4% of patients. Among the patients with colitis, 85% received systemic corticosteroids and 10% received another immunosuppressant (infliximab). Colitis resolved in 60% of patients, with a median time to resolution of 77 days (range, 6 – 675 days).

Immune-related nephritis

Immune-related nephritis occurred in 1.7% of patients receiving retifanlimab, including 0.5% of patients with Grade 2, 0.9% of patients with Grade 3 and 0.3% of patients with Grade 4. The median time to onset of nephritis was 170 days (range, 15 – 515 days). Nephritis led to discontinuation of retifanlimab in 0.9% of patients. Among the patients with nephritis, 72.7% received systemic corticosteroids. Nephritis resolved in 36.4% of patients, with a median time to resolution of 22.5 days (range, 9 – 136 days).

Immune-related endocrinopathies

Hypothyroidism occurred in 10.1% of patients receiving retifanlimab, including 4.9% of patients with Grade 2 and 0.2% of patients with Grade 3. The median time to onset of hypothyroidism was 85 days (range, 1 – 577 days). None of the events led to discontinuation of retifanlimab. Hypothyroidism resolved in 27.3% of patients, with a median time to resolution of 56.5 days (range, 2 – 224 days).

Hyperthyroidism occurred in 6.1% of patients receiving retifanlimab, including 2.1% of patients with Grade 2. The median time to onset of hyperthyroidism was 56 days (range, 8 – 575 days). None of the events led to discontinuation of retifanlimab. Hyperthyroidism resolved in 60% of patients, with a median time to resolution of 55.5 days (range, 14 – 295 days).

Hypophysitis occurred in 0.5% of patients receiving retifanlimab, including 0.3% of patients with Grade 2 and 0.2% of patients with Grade 3. The median time to onset of hypophysitis was 308 days (range, 266 – 377 days). Hypophysitis led to discontinuation of retifanlimab in 0.2% of patients. Hypophysitis resolved in 33.3% of patients, with a time to resolution of 6 days.

Adrenal insufficiency occurred in 0.8% of patients receiving retifanlimab, including 0.5% of patients with Grade 2 and 0.3% of patients with Grade 3. The median time to onset of adrenal insufficiency was 197 days (range, 146 – 275 days). None of the events led to discontinuation of retifanlimab. Adrenal insufficiency resolved in 20% of patients, with a time to resolution of 12 days.

Type 1 diabetes mellitus (Grade 3) occurred in 0.3% of patients receiving retifanlimab. The median time to onset of type 1 diabetes mellitus was 156.5 days (range, 29 – 284 days). Type 1 diabetes mellitus led to discontinuation of retifanlimab in 0.2% of patients. Type 1 diabetes mellitus resolved in all patients, with a time to resolution of 6 days.

Immune-related hepatitis
Immune-related hepatitis occurred in 3.4% of patients receiving retifanlimab, including 1.1% of patients with Grade 2, 2.1% of patients with Grade 3 and 0.2% of patients with Grade 4. The median time to onset of hepatitis was 53.5 days (range, 8 – 580 days). Hepatitis led to discontinuation of retifanlimab in 1.2% of patients. Among the patients with hepatitis, 81.8% of patients received systemic corticosteroids and 4.5% of patients received another immunosuppressant (mycophenolate mofetil). Hepatitis resolved in 45.5% of patients, with a median time to resolution of 23 days (range, 6 – 104 days).

Immune-related skin reactions
Immune-related skin reactions occurred in 8% of patients receiving retifanlimab, including 6.4% of patients with Grade 2, 1.2% of patients with Grade 3 and 0.2% of patients with Grade 4. The median time to onset of skin reactions was 85.5 days (range, 2 – 628 days). Skin reactions led to discontinuation of retifanlimab in 0.5% of patients. Among the patients with skin reactions, 34.6% of patients received systemic corticosteroids. Skin reactions resolved in 71.2% of patients, with a median time to resolution of 40 days (range, 3 – 470 days).

Infusion-related reactions

Infusion-related reactions occurred in 7.2% of patients, including 2.6% of patients with Grade 2 and 0.5% of patients with Grade 3. Infusion-related reactions led to discontinuation of retifanlimab in 0.3% patients.

Immunogenicity

Anti-drug antibodies (ADAs) were tested in 104 patients with MCC who received ZYNYZ. The incidence of retifanlimab-induced ADAs was 2.9% (3/104) using a bridging enzyme-linked immunosorbent assay after a median exposure time of 169 days. Neutralising antibodies were detected in 2 of the 3 patients presenting with ADAs that occurred during treatment. The effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety of use and/or the efficacy of retifanlimab-based products is unknown.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

L01FF10

Mechanism of action

Retifanlimab is an immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T-cell function such as proliferation, cytokine secretion and cytotoxic activity. Retifanlimab binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2 and potentiates T-cell activity.

Pharmacodynamics

Clinical efficacy

The efficacy of retifanlimab was studied in the POD1UM201 study, an open-label, singlearm, multiregional study that enrolled patients with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression, severe hepatic or renal impairment, clinicly significant cardiac disease, history of organ transplant, or Eastern Cooperative Oncology Group (ECOG) performance score (PS) ≥ 2 were ineligible. Patients who were HIV positive, with an undetectable viral load, a CD4+ count ≥ 300 cells/microliter and receiving antiretroviral therapy were eligible.

Patients received retifanlimab 500 mg every 4 weeks until disease progression or unacceptable toxicity for a maximum of 2 years. Assessment of efficacy was performed every 8 weeks for the first year of therapy and 12 weeks thereafter. The major efficacy outcome measure of confirmed objective response rate, and duration of response were assessed by an independent central review committee according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. All ongoing responses were followed for a minimum of 12 months.

A total of 101 patients were analysed for efficacy. The median age of enrolled patients was 71.0 years (range, 38 - 90 years) with 39 (38.6%) age 75 or older; 67.3% of patients were male, all but one patient with reported race were Caucasian and the Eastern Cooperative Oncology Group performance status was 0 (73.3%) or 1 (26.7%). Thirty seven percent of patients were reported to have had prior radiotherapy and 68.3% had prior surgery. Ninety percent of patients had metastatic disease and 10% of patients had locally advanced disease. One patient was HIV positive. The majority of tumour samples tested (72.3%) were positive for Merkel cell polyomavirus (MCPyV).

Efficacy results at the final analysis are summarized in Table 3. The median duration of treatment was 10.3 months (range, 1 day – 24.8 months).

Table 3: Efficacy results in POD1UM-201 study for patients with metastatic or recurrent locally advanced MCC

Endpoint	ZYNYZ (N = 101)
Objective response rate	
Objective response rate (95% CI)	54.5% (44.2, 64.4)
Complete response	17.8%
Partial response	36.6%
Duration of response	
Median in months (95% CI)	NE (22.9, NE)
Minimum, maximum (months)	1.1, 55.3

CI = confidence interval; NE = not estimable; + denotes ongoing response.
Based on final analysis, with a median duration of follow-up of22.2 months (range, 1.1 – 55.3 months).

Efficacy and MCPyV status

The objective response rate (ORR) in patients with MCC with PD-L1 expression ≥ 1% (n=83) was 59.0% (47.7; 69.7), and in patients with MCC with PD-L1 expression < 1% or missing (n=18), 33.3% (13.3; 59.0).The ORR in patients with MCC with Merkel cell polyomavirus (MCPyV) positive status (n = 73) was 53.4% (41.4, 65.2) and in patients with MCC with MCPyV negative or missing status (n = 28) was 57.1% (37.2, 75.5).

Elderly population

Of the 101 patients treated with retifanlimab in the efficacy population, 76.2% (77/101) were 65 years or older, and 38.6% (39/101) were 75 years or older. Objective response rates in these age groups were 57.1% (95% CI: 45.4, 68.4) and 51.3% (95% CI: 34.8, 67.6), respectively.

Pharmacokinetics

The pharmacokinetics (PK) of retifanlimab were characterised using a population pharmacokinetics analysis with concentration data collected from 634 patients with various cancers who received retifanlimab doses of 1, 3, 10 mg/kg every 2 weeks, 375 mg every 3 weeks, or 3 mg/kg, 10 mg/kg, 500 mg and 750 mg every 4 weeks. The AUC was dose proportional in the studied dose range. The geometric mean (CV%) of C_{max} and AUC at steady state for the recommended 500 mg every 4 weeks dose were 193 mg/L (24.1%) and 2190 day*mg/L (32.4%).

Absorption

Not applicable

Distribution

The geometric mean value (CV%) for volume of distribution at steady state is 6.1 L (20.2%).

Metabolism

The metabolic route of retifanlimab has not been characterised. Retifanlimab is expected to be catabolised through protein degradation processes.

Elimination

A geometric mean (CV%) clearance of 0.314 L/day (36%), without accounting for the time-varying part of the clearance, with a half-life of 14.6 days (31.5%) and 18.7 days (28.7%), after first-dose and at steady-state, respectively, were estimated in the population pharmacokinetic analyses.

Pharmacokinetics in specific patient groups

The following factors are not expected to have clinically important effects on the pharmacokinetics of retifanlimab: age (range: 18 to 94 years), weight (35 to 133 kg), sex, race (White, Black, Asian), or tumour burden.

Renal impairment

The effect of renal impairment on the clearance of retifanlimab was evaluated by population pharmacokinetic analyses in patients with mild (n = 277) or moderate (n = 142) renal impairment (eGFR between 89 and 30 mL/min/1.73m^2; n = 419) compared to patients with normal renal function (eGFR ≥ 90 mL/min/1.73m^2; n = 200). No clinically important differences were found in the clearance of retifanlimab. There are limited data in patients with severe renal impairment (n = 4, lowest eGFR 26.0 mL/min/1.73m^2). Retifanlimab has not been studied in patients with end-stage renal disease.

Hepatic impairment

The effect of hepatic impairment on the clearance of retifanlimab was evaluated by population pharmacokinetic analyses in patients with mild (n = 78; TB > ULN to 1.5 ULN or AST > ULN) hepatic impairment compared to patients with normal (n = 555; TB and AST ≤ ULN) hepatic function. No clinically important differences were found in the clearance of retifanlimab. There are limited data in patients with moderate (n = 1; TB between 1.5 and 3.0 times ULN and any AST) hepatic impairment. Retifanlimab has not been studied in patients with severe hepatic impairment (TB between 3.0 and 10 times ULN and any AST).

Preclinical data

Preclinical data from repeated dose toxicity studies in cynomolgus monkeys treated intravenously at doses of 5, 20, or 100 mg/kg once weekly in a 13-week study have not revealed a particular risk for humans. The maximum no observable adverse effect dose (NOAEL) was 100 mg/kg, which corresponds to 20 times the therapeutic exposure in humans.

No studies have been performed to assess the potential of retifanlimab for carcinogenicity or genotoxicity.

Animal reproduction and development toxicity studies have not been conducted with retifanlimab. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the foetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increase in foetal loss; therefore, potential risks of administering retifanlimab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, foetal exposure to retifanlimab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and/or diluents except those mentioned in section “Handling Notes”. Other medicinal products should not be co-administered through the same infusion line.

Shelf life

This medicine must not be used after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The concentrate does not contain a preservative. For microbiological reasons, the concentrate should be used for dilution immediately after opening.

Shelf life after dilution

The diluted preparation for infusion does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2 - 8°C and 8 hours at room temperature (20 ºC to 25 ºC). For microbiological reasons, the ready-to-use preparation should be used immediately after

dilution. If this is not possible, in-use storage times and conditions of the ready-to-use preparation are the responsibility of the user and should normally be no longer than 24 hours at 2 - 8°C or 8 hours at room temperature (20 °C to 25 °C), unless the dilution has taken place in controlled and validated aseptic conditions, see section “Handling Notes”.

Special precautions for storage

Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Store the container in the original carton in order to protect from light.
Keep out of the reach of children.

Handling Notes

Preparation and administration

- Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. Retifanlimab is a clear to slightly opalescent, colourless to pale yellow solution, free of visible particles. Discard the vial if the solution is cloudy, discoloured or visible particles are observed.
- Do not shake the vial.
- Withdraw 20 mL (500 mg) of retifanlimab concentrate from the vial and transfer into an intravenous infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection to prepare a diluted solution with a final concentration between 1.4 mg/mL to 10 mg/mL. Use polyvinylchloride (PVC) and di-2-ethylhexyl phthalate (DEHP), polyolefin copolymer, polyolefin with polyamide, or ethylene vinyl acetate infusion bags.
- Mix the diluted solution by gentle inversion. Do not shake the infusion bag.
- From a microbiological point of view, the diluted solution, once prepared, should be used immediately. If not used immediately, chemical and physical in-use stability has been demonstrated:
    - For 8 hours at room temperature (20 °C to 25 °C) (including infusion time).
      OR
    - For 24 hours under refrigeration (2 °C to 8 °C). If refrigerated, allow the diluted solution to come to room temperature prior to administration. The diluted solution must be administered within 4 hours (including infusion time) once it is removed from the refrigerator. Do not freeze.
- Discard if the diluted solution is discoloured or contains extraneous particulate matter other than trace amounts of translucent to white particles.
- Administer the retifanlimab solution by intravenous infusion over 30 minutes using a sterile, non-pyrogenic, low-protein binding polyethersulfone, polyvinylidene fluoride, or cellulose acetate 0.2 micron to 5 micron in-line or add-on filter or 15 micron mesh in-line or add-on filter.

- Do not co-administer other medicinal products through the same infusion line.

Disposal

- Retifanlimab is for single use; discard any unused portion left in the vial.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

70012

Packs

ZYNYZ 500 mg/20 ml: Carton of 1 vial for single use (A)
ZYNYZ is available in a 20 mL Type I glass vial, closed with a FluroTec-coated chlorobutyl rubber stopper, aluminium seal and plastic flip-off cap, containing 20 mL concentrate.

Marketing authorisation holder

Incyte Biosciences International Sàrl, 1110 Morges

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