ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

ZYNYZ 500 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 20 mL concentrate contains 500 mg of retifanlimab.

Each mL of concentrate contains 25 mg of retifanlimab.

Retifanlimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

Posology

The recommended dose is 500 mg retifanlimab every 4 weeks administered as an intravenous infusion over 30 minutes. 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 4.4 and 4.8).

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.
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.

Adverse reaction	Severity[a]	Dose modification
	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.
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.

Adverse reaction	Severity[a]	Dose modification
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 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.

Patient card

All prescribers of ZYNYZ should be familiar with and inform the patients about the patient card explaining what to do should they experience any symptom of immune-related adverse reactions. The patient card will be provided to each patient treated with retifanlimab.

Special populations

Elderly
No dose adjustment is needed for patients who are aged 65 years or over (see sections 5.1 and 5.2).

Renal impairment
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 5.2).

Hepatic impairment
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 5.2).

Paediatric population
There is no relevant use of retifanlimab in children and adolescents below the age of 18 years with Merkel cell carcinoma.

Method of administration

ZYNYZ is for intravenous use. It must be diluted and 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.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Immune-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 4.8). 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 4.8). 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 4.8). 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 4.8). 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 4.8). 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 4.8). 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 4.8). Patients should be monitored for changes in renal function and managed with retifanlimab treatment modifications and corticosteroids (see section 4.2).

Immune-related skin reactions
Immune-related skin reactions, such as toxic epidermal necrolysis, have been reported in patients receiving retifanlimab (see section 4.8). 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
Clinically significant, immune-related adverse reactions were reported in patients treated with retifanlimab in clinical studies including: uveitis, arthritis, myositis, demyelinating polyneuropathy (e.g. Guillain Barré syndrome), pancreatitis and myocarditis (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with retifanlimab treatment modifications as described in section 4.2.

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 4.2). 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 4.8).

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.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 4.2 and 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential should use effective contraception during treatment with retifanlimab and for at least 4 months after the last dose of retifanlimab.

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 5.3).

Breast-feeding
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 during the first few days after birth; which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. For this specific period, a decision should be made whether to discontinue/abstain from retifanlimab therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman. Afterwards, retifanlimab could be used during breast-feeding if clinically needed.

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.

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

4.8 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 (35.4%), rash (18.8%), diarrhoea (18.6%), anaemia (16.2%), pruritus (15.9%), arthralgia (13.3%), constipation (13.3%), nausea (13.3%), pyrexia (13.1%) and decreased appetite (12.6%). Adverse reactions were serious in 11.7% of patients; most serious adverse reactions were immune-related adverse reactions.

ZYNYZ was permanently discontinued due to adverse reactions in 8% of patients; most of them were immune-related events.

Tabulated list of adverse reactions
The safety of retifanlimab has been evaluated in 452 patients with advanced solid malignancies who received the recommended 500 mg every 4 weeks dose, including 107 patients with metastatic or recurrent locally advanced MCC. Median duration of treatment was 5.4 months (range, 1 day

– 27 months). The frequencies included below are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.
These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence.

Table 2: Adverse reactions in patients treated with retifanlimab (N = 452)

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]

System organ class	Frequency of all grades	Frequency of grades 3-4
Hepatobiliary disorders	**Common** Hepatocellular injury Hepatitis[h] **Uncommon** Hyperbilirubinaemia Cholangitis	**Uncommon** Hepatitis[h] 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 Renal failure **Uncommon** 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] **Uncommon** Blood bilirubin increased Lipase increased Blood creatinine increased Amylase 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

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

[k] Includes asthenia and fatigue
[l] Includes transaminases increased, alanine aminotransferase increased and aspartate 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 452 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 4.2.

Immune-related adverse reactions (see section 4.4)
Immune-related pneumonitis
Immune-related pneumonitis occurred in 3.1% of patients receiving retifanlimab, including 1.3% 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 100 days (range, 43 – 673 days). Pneumonitis led to discontinuation of retifanlimab in 0.2% of patients. Among the patients with pneumonitis, 71.4% received systemic corticosteroids. Pneumonitis resolved in 78.6% of patients, with a median time to resolution of 37 days (range, 9 – 104 days).

Immune-related colitis
Immune-related colitis occurred in 2.7% of patients receiving retifanlimab, including 1.1% of patients with Grade 2, 0.4% of patients with Grade 3 and 0.2% of patients with Grade 4. The median time to onset of colitis was 165.5 days (range, 11 – 749 days). Colitis led to discontinuation of retifanlimab in 0.9% of patients. Among the patients with colitis, 75% received systemic corticosteroids and 8.3% received another immunosuppressant (infliximab). Colitis resolved in 66.7% of patients, with a median time to resolution of 83.5 days (range, 15 – 675 days).

Immune-related nephritis
Immune-related nephritis occurred in 2% of patients receiving retifanlimab, including 0.4% of patients with Grade 2, 1.1% of patients with Grade 3 and 0.4% of patients with Grade 4. The median time to onset of nephritis was 176 days (range, 15 – 515 days). Nephritis led to discontinuation of retifanlimab in 1.1% of patients. Among the patients with nephritis, 66.7% received systemic corticosteroids. Nephritis resolved in 44.4% of patients, with a median time to resolution of 22.5 days (range, 9 – 136 days).

Immune-related endocrinopathies
Hypothyroidism occurred in 10.2% of patients receiving retifanlimab, including 4.9% of patients with Grade 2. The median time to onset of hypothyroidism was 88 days (range, 1 – 505 days). None of the events led to discontinuation of retifanlimab. Hypothyroidism resolved in 32.6% of patients, with a median time to resolution of 56 days (range, 2 – 224 days).

Hyperthyroidism occurred in 5.8% of patients receiving retifanlimab, including 2.7% of patients with Grade 2. The median time to onset of hyperthyroidism was 55.5 days (range, 8 – 575 days). None of the events led to discontinuation of retifanlimab. Hyperthyroidism resolved in 61.5% of patients, with a median time to resolution of 74 days (range, 15 – 295 days).

Hypophysitis occurred in 0.7% of patients receiving retifanlimab, including 0.4% 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 0.9% of patients receiving retifanlimab, including 0.4% of patients with Grade 2 and 0.4% of patients with Grade 3. The median time to onset of adrenal insufficiency was 220.5 days (range, 146 – 275 days). None of the events led to discontinuation of retifanlimab. Adrenal insufficiency resolved in 25% of patients, with a time to resolution of 12 days.

Type 1 diabetes mellitus presenting as diabetic ketoacidosis (Grade 3) occurred in 0.2% of patients receiving retifanlimab. The time to onset of diabetic ketoacidosis was 284 days. The event did not lead to discontinuation of retifanlimab and resolved with a time to resolution of 6 days.

Immune-related hepatitis
Immune-related hepatitis occurred in 3.5% of patients receiving retifanlimab, including 0.9% of patients with Grade 2, 2.4% of patients with Grade 3 and 0.2% of patients with Grade 4. The median time to onset of hepatitis was 70.5 days (range, 8 – 580 days). Hepatitis led to discontinuation of retifanlimab in 1.5% of patients. Among the patients with hepatitis, 81.3% of patients received systemic corticosteroids and 6.3% of patients received another immunosuppressant (mycophenolate mofetil). Hepatitis resolved in 56.3% of patients, with a median time to resolution of 22 days (range, 6 – 104 days).

Immune-related skin reactions
Immune-related skin reactions occurred in 9.5% of patients receiving retifanlimab, including 8% of patients with Grade 2, 1.1% of patients with Grade 3 and 0.2% of patients with Grade 4. The median time to onset of skin reactions was 86 days (range, 2 – 589 days). Skin reactions led to discontinuation of retifanlimab in 0.7% of patients. Among the patients with skin reactions, 32.6% of patients received systemic corticosteroids. Skin reactions resolved in 72.1% of patients, with a median time to resolution of 37 days (range, 3 – 470 days).

Infusion-related reactions
Infusion-related reactions occurred in 6.2% of patients, including 2.2% of patients with Grade 2 and 0.4% of patients with Grade 3. Infusion-related reactions led to discontinuation of retifanlimab in 0.4% patients.

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, PD-1/PD-L1 (Programmed cell death protein 1/death ligand 1) inhibitors. 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.

Pharmacodynamic effects

Immunogenicity
Anti-drug antibodies (ADA) were uncommonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety
The efficacy and safety of retifanlimab was studied in the POD1UM-201 study, an open-label, single-arm, 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, clinically 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 71.1 years (range, 38 - 90 years) with 39 (39%) age 75 or older; 67.3% of patients were male, all but one patient 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. One patient was HIV-positive. The majority of tumour samples tested (72.3%) were positive for Merkel cell polyomavirus (MCPyV).

Efficacy results 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)	53.5% (43.3, 63.5)
Complete response	16.8%
Partial response	36.6%
Duration of response	
Median in months (95% CI)	25.3 (14.2, NE)
Minimum, maximum (months)	1.1, 38.7+

CI = confidence interval; NE = not estimable; + denotes ongoing response.
Median duration of follow-up: 17.6 months (range, 1.1 – 38.7 months).

Efficacy and PD-L1/MCPyV status
Clinical activity was observed regardless of PD-L1 or MCPyV status. Table 4 summarises the objective response rates by tumour PD-L1 expression and MCPyV status of chemotherapy-naïve MCC patients with central biomarker results in the POD1UM-201 study.

Table 4: Objective response rates by tumour PD-L1 expression and MCPyV status

	ZYNYZ Objective response rates (95% CI) N = 101
PD-L1 expression[a] at cut-off of ≥ 1%	
Positive (n = 83)	57.8% (46.5, 68.6)
Negative or missing (n = 18)	33.3% (13.3, 59.0)
MCPyV status	
Positive (n = 73)	52.1% (40, 63.9)
Negative, equivocal, or missing (n = 28)	57.1% (37.2, 75.5)

MCPyV = Merkel cell polyomavirus.
[a] PD-L1 expression was determined by IHC using Combined Positive Score (CPS) interpretation.

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 55.8% (95% CI: 44.1, 67.2) and 48.7% (95% CI: 32.4, 65.2), respectively.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with ZYNYZ in all subsets of the paediatric population for the treatment of MCC. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

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%).

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

Biotransformation
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.

Special Populations
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, 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 (TB between 3.0 and 10 times ULN and any AST) hepatic impairment.

5.3 Preclinical safety data

No findings of toxicological significance were observed in monkeys in studies of up to 13 weeks duration at exposures sufficiently in excess compared to the clinical exposure at the recommended dose of 500 mg retifanlimab every 4 weeks.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (for pH adjustment) (E262)
Acetic acid, glacial (E260)
Sucrose
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and/or diluents except those mentioned in section 6.6. Other medicinal products should not be co-administered through the same infusion line.

6.3 Shelf life

Unopened vial
2 years

After dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 ºC to 8 ºC and 8 hours at room temperature (20 ºC to 25 ºC).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2 ºC to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial, closed with a FluroTec-coated chlorobutyl rubber stopper, aluminium seal and plastic flip-off cap, containing 20 mL concentrate.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1800/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

MacroGenics
9704 Medical Center Drive
Rockville, MD 20850
United States

Name and address of the manufacturer responsible for batch release

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to the launch of ZYNYZ in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication

media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The purpose of the educational programme is to minimise the risk of immune-related adverse reactions and optimise the risk-benefit balance of ZYNYZ. The aim of this tool is to ensure that information regarding the patient's treatment with ZYNYZ and its important risks of immune-related adverse reactions are held by the patient at all times and reaches the relevant healthcare professionals as appropriate. The information on the patient card is focused on signs and symptoms of immune-related adverse reactions and the best course of action to be taken by the patient and relevant healthcare professional.

The MAH shall ensure that in each Member State where ZYNYZ is marketed, all healthcare professionals who are expected to prescribe ZYNYZ have access to/are provided with the following educational materials:

- Package leaflet
- Patient card

The **patient card** shall contain the following key messages:

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using ZYNYZ
- That ZYNYZ treatment may increase the risk of immune-related adverse reactions
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
- Contact details of their ZYNYZ prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ZYNYZ 500 mg concentrate for solution for infusion
retifanlimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 20 mL concentrate contains 500 mg of retifanlimab (25 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: E262, E260, sucrose, E433, water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
500 mg/20 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution.
Read the package leaflet before use.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1800/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

ZYNYZ 500 mg sterile concentrate
retifanlimab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg/20 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ZYNYZ 500 mg concentrate for solution for infusion
retifanlimab

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

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will provide you with a patient card. Be sure to keep this card with you while undergoing treatment with ZYNYZ.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ZYNYZ is and what it is used for

ZYNYZ contains the active substance retifanlimab, a monoclonal antibody (a protein that recognises and attaches to a specific target substance in the body). ZYNYZ helps your immune system fight your cancer.

ZYNYZ is used in adults to treat **Merkel cell carcinoma**, a rare type of **skin cancer**. It is given when the cancer has spread or returned and cannot be treated with surgery or radiation.

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

You must not be given ZYNYZ if you
- are allergic to retifanlimab or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor or nurse before you are given ZYNYZ if you have:
- an illness where the body's immune system attacks its own cells
- had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells
- lung or breathing problems
- liver or kidney problems
- diabetes

Tell your doctor immediately if you have any of the following symptoms during treatment or if they get worse:
- **lung inflammation** (pneumonitis) such as breathing difficulties, chest pain or new or worsening cough.

- **bowel inflammation** (colitis) such as frequent diarrhoea often with blood and/or mucus, more bowel movements than usual, stools that are bloody, black or tarry and severe abdominal pain or tenderness.
- **liver inflammation**. Symptoms include persistent nausea or vomiting, loss of appetite, pain on the right side of your stomach, eye and/or skin yellowing, drowsiness, dark-coloured urine, bleeding or bruising more easily than normal.
- **hormone gland problems** (including the pituitary, thyroid and adrenal glands) that may affect how these glands work. Symptoms include fast heartbeat, dizziness, fainting, extreme tiredness, persistent or unusual headaches, weight change, hair loss, feeling cold or constipation.
- **type 1 diabetes or diabetic ketoacidosis**. Symptoms of diabetes include feeling more hungry or thirsty than usual, frequent urination, weight loss, feeling tired or sick. Symptoms of diabetic ketoacidosis include difficulty thinking clearly, sleepiness, stomach pain, fast and deep breathing, breath that smells sweet or fruity, sweet or metallic taste in the mouth or a different odour to urine or sweat.
- **kidney inflammation**. Symptoms include decreased volume of urine, foamy urine, passing blood or traces of blood in the urine that may change its colour, swollen ankles or loss of appetite.
- **skin problems** that can lead to a severe skin reaction known as toxic epidermal necrolysis and Stevens-Johnson syndrome. Symptoms include rash, itching, skin blistering or ulcers in the mouth or in the lining of the nose, throat or genital area.
- **inflammation in other parts of the body** such as eyes (changes in eyesight), joints, muscles, nerves, pancreas (symptoms include abdominal pain, nausea or vomiting), or of the heart muscle.
- **infusion-related reactions** such as chills, shaking, rigor, fever, itching, rash, flushing or swollen face, shortness of breath or wheezing, feeling dizzy or faint.

If you have any of the above-mentioned symptoms during treatment, do not try to treat your symptoms with other medicines on your own. Your doctor may:
- give you other medicines to prevent complications and reduce your symptoms,
- monitor you,
- withhold the next dose of ZYNYZ,
- stop your treatment or
- slow or stop your infusion depending on the severity of the reaction, if you have an infusion-related reaction when you receive ZYNYZ.

Please note that the above listed symptoms are **sometimes delayed** and may occur weeks or months after your last dose.

Complications of solid organ transplant rejection, including graft-versus-host disease, in patients who have received a bone marrow (stem cell) transplant that uses donor stem cells can lead to death. They may occur if you undergo transplantation either before or after treatment with ZYNYZ. Your doctor will monitor you for these complications.

Children and adolescents
ZYNYZ should not be given to children and adolescents under 18 years of age because it has not been studied in this patient group.

Other medicines and ZYNYZ
Tell your doctor or nurse if you are using, have recently used or might use any other medicines. This applies in particular to medicines that suppress your immune system, such as corticosteroids, which may disrupt the effect of ZYNYZ. Once you are treated with ZYNYZ, your doctor may prescribe corticosteroids to reduce side effects that you may have during treatment. This will not impact the effect of the medicine.

Contraception
Women who could become pregnant must use effective contraception during treatment and for minimum 4 months after the last ZYNYZ dose.

Pregnancy
You must not be given ZYNYZ if you are pregnant unless your doctor specifically recommends it. ZYNYZ can cause harmful effects or death to your unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Breast-feeding
It is not known if ZYNYZ passes into breast milk. A risk to the breast-feeding newborns/infants cannot be excluded. Ask your doctor for advice if you are breast-feeding.

Driving and using machines
ZYNYZ may have a minor influence on the ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.

ZYNYZ contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose unit, that is to say essentially 'sodium-free.' However, before ZYNYZ is given to you, it is mixed with a solution that may contain sodium. Talk to your doctor if you are on a low-salt diet.

3. How ZYNYZ is given

ZYNYZ will be given to you in a hospital or clinic, supervised by a doctor experienced in cancer treatment.

The recommended dose of ZYNYZ is 500 mg every 4 weeks.

Your doctor will give you ZYNYZ as a drip into a vein (intravenous infusion) which will last about 30 minutes.

Your doctor will decide how many treatments you need.

If you miss an appointment to receive ZYNYZ
It is very important that you do not miss a dose of this medicine. Contact your doctor or hospital immediately to reschedule your appointment.

If you stop receiving ZYNYZ
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with ZYNYZ without the agreement of your doctor.

Patient card
Important information from this package leaflet can be found in the patient card you have been given by your doctor. It is important that you keep this patient card and show it to your partner or caregivers.

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

4. Possible side effects

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

ZYNYZ can have serious side effects, which can sometimes become life-threatening and can lead to death. These side effects may happen at any time during treatment, or even after your treatment has ended. You may get more than one side effect at the same time (See section 2, "Warnings and precautions" for symptoms).

Tell your doctor immediately if you have any of the following **serious side effects**:

Common (may affect up to 1 in 10 people):
- lung inflammation *(pneumonitis)*
- bowel inflammation *(colitis)*
- liver inflammation *(hepatitis)*
- liver cell injury *(hepatocellular injury)*
- sudden kidney damage *(acute kidney failure)*
- kidney failure *(renal failure)*
- infusion-related reactions that can cause symptoms such as chills, shaking or fever, itching or rash, flushing or swollen face, being short of breath or wheezing, feeling dizzy or nausea.

Uncommon (may affect up to 1 in 100 people)
- inflammation of the pituitary gland in the base of the brain *(hypophysitis)*
- acid in the blood produced from diabetes *(diabetic ketoacidosis)*
- damage to nerves causing numbness and weakness *(polyneuropathy)*
- pinched nerve caused by damage to the root of the nerve(s) in the spine *(radiculopathy)*
- nerve damage to voice box which is used for breathing, swallowing and talking *(vocal cord paralysis)*
- inflammation of the eyes *(uveitis)*
- inflammation of the cornea or the clear tissue on the front of the eye *(keratitis)*
- inflammation of the covering of the heart which often causes sharp chest pain *(pericarditis)*
- inflammation of the heart muscle *(myocarditis)*
- inflammation of the pancreas *(pancreatitis)*

Other side effects may occur with the following frequencies:

Very common (may affect more than 1 in 10 people):
- decrease in the number of red blood cells *(anaemia)*
- decreased appetite
- diarrhoea
- nausea
- constipation
- rash
- itching of the skin *(pruritus)*
- joint pain *(arthralgia)*
- tiredness *(fatigue)*
- fever *(pyrexia)*

Common (may affect up to 1 in 10 people):
- underactive thyroid gland *(hypothyroidism)*
- overactive thyroid gland *(hyperthyroidism)*
- abnormal sensation such as tingling or numbness of the hands or feet *(paraesthesia)*
- increased blood level of liver enzymes, including alanine aminotransferase, aspartate aminotransferase
- increased blood levels of bilirubin
- increased blood levels of creatinine
- increased blood levels of thyroid stimulating hormone
- increased level of amylase, an enzyme that breaks down starch
- increased levels of lipase, an enzyme that breaks down fats

Uncommon (may affect up to 1 in 100 people):
- decreased secretion of hormones produced by the adrenal glands *(adrenal insufficiency)*
- thyroid gland inflammation *(thyroiditis)*
- inflammation of the bile ducts *(cholangitis)*
- increased blood levels of bilirubin causing yellowing of the eyes and skin *(hyperbilirubinaemia)*
- joint inflammation *(arthritis)*
- muscle inflammation *(myositis)*
- inflammation of the tissue between the muscle and skin which may cause skin swelling *(eosinophilic fasciitis)*
- inflammation of the muscles causing pain or stiffness *(polymyalgia rheumatica)*
- decreased blood levels of thyroid stimulating hormone

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

5. How to store ZYNYZ

ZYNYZ will be given to you in a hospital or clinic and the healthcare professionals will be responsible for its storage.

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

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

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Store in the original package in order to protect from light.

Once prepared, the infusion may be stored for up to 24 hours at 2 °C to 8 °C or 8 hours at 20 °C to 25 °C, from time of preparation until the end of infusion.

Do not store any unused medicine for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What ZYNYZ contains
- The active substance is retifanlimab.
  One mL of concentrate for solution for infusion contains 25 mg of retifanlimab.
  One vial of 20 mL of concentrate contains 500 mg of retifanlimab.
- The other ingredients are sodium acetate trihydrate (E262), acetic acid (glacial) (E260), sucrose, polysorbate 80 (E433), water for injections. See section 2 “ZYNYZ contains sodium".

What ZYNYZ looks like and contents of the pack
ZYNYZ is a clear to slightly opalescent, colourless to pale yellow concentrate for solution for infusion (sterile concentrate).

It is available in a pack containing 1 glass vial of 20 mL of concentrate.

Marketing Authorisation Holder and Manufacturer
Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

This leaflet was last revised in {**MM/YYYY**}

Other sources of information

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

The following information is intended for healthcare professionals only:

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 at (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 coadminister other medicinal products through the same infusion line.

Disposal

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