Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

Patient enrolment in this EAMS has been closed on 12 June 2017.

As some patients may still be on treatment, the safety information in this Treatment protocol has been updated (sections 4.2, 4.4 and 4.8) on 19 June 2017.

Contact information regarding queries on the use of this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Atezolizumab 1,200 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 20 mL concentrate contains 1,200 mg atezolizumab, corresponding to a concentration before dilution of 60 mg/mL.

For dilution and other handling recommendations, see section 6.6.

Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to slightly yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after disease progression following one prior platinum-containing chemotherapy regimen regardless of its setting (neoadjuvant, adjuvant, or metastatic).

4.2 Posology and method of administration

Atezolizumab must be administered under the supervision of a qualified healthcare professional.

Posology
The recommended dose of atezolizumab is 1,200 mg administered intravenously every three weeks.

Duration of treatment
It is recommended that patients are treated with atezolizumab until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

Delayed or missed doses
If a planned dose of atezolizumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

Dose modifications during treatment
No dose reductions of atezolizumab are recommended. For dose delay or discontinuation (see also sections 4.4 and 4.8).

Table 1 Dose modification advice for specified Adverse Drug Reactions

Adverse Reaction	Severity	Treatment Modification
Pneumonitis	Grade 2	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Hepatitis	Grade 2: (ALT or AST >3-5x upper limit of normal [ULN] *or* blood bilirubin >1.5–3x ULN)	If persists > 5-7 days, withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST >5x ULN *or* blood bilirubin >3x ULN)	Permanently discontinue atezolizumab
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥4 stools/day over baseline) *or* Symptomatic Colitis	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day
	Grade 4 Diarrhoea *or* Colitis (life threatening; urgent intervention indicated)	Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold atezolizumab *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by methimazole or equivalent and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold atezolizumab

		Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue atezolizumab
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose >250-500 mg/dL)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related Reactions	Grade 1	Reduce infusion rate to half Once the event has resolved, wait for 30 min while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to original rate
	Grade 2	Withhold atezolizumab Restart at half of the infusion rate only after the symptoms have resolved
	Grade 3 or 4	Permanently discontinue atezolizumab
Rash	Grade 3	Withhold atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day
	Grade 4	Permanently discontinue atezolizumab
Myasthenic syndrome / myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue atezolizumab
Myocarditis	Grade 2	Withhold atezolizumab Treatment may be resumed when myocarditis is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2x ULN) *or* Grade 2 or 3 pancreatitis	Withhold atezolizumab Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAEv.4).

Atezolizumab should be permanently discontinued:

- For Grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones
- For any recurrent event at Grade ≥ 3 severity
- If a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date
- If a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatment related toxicity beyond 12 weeks after adverse reaction onset date.

Special populations

Paediatric population
The safety and efficacy of atezolizumab in children and adolescents aged below 18 years have not been established. No data are available.

Elderly people
Based on a population pharmacokinetic analysis, no dose adjustment of atezolizumab is required in patients ≥ 65 years of age.

Renal impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment.

Hepatic impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. There are no data in patients with moderate or severe hepatic impairment.

Method of administration

Atezolizumab is for intravenous use. Atezolizumab infusions must not be administered as an intravenous push or bolus.

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

The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system were observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs

and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis
Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1-2 mg/kg prednisone or equivalent per day should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-related hepatitis
Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis.

Patients with abnormal liver function tests (LFTs) defined as Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 3x ULN or > 5x ULN in case of liver involvement at baseline were excluded during clinical trials.

Aspartate aminotransferase, alanine aminotransferase and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

Treatment with atezolizumab should be withheld if Grade 2 (ALT or AST >3-5x ULN or blood bilirubin >1.5-3x ULN) persists for more than 5-7 days, and 1-2 mg/kg prednisone or equivalent per day should be started. If LFTs improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST >5.0x ULN or blood bilirubin >3x ULN).

Immune-related colitis
Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis.
Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1-2 mg/kg prednisone or equivalent per day should be started. For Grade 3 diarrhoea or colitis, treatment with IV corticosteroids (1-2 mg/kg/day methylprednisolone or equivalent) should be started and converted to oral corticosteroids (prednisone 1-2 mg/kg or equivalent per day) after improvement. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Immune-related endocrinopathies
Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab (see section 4.8).
Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For

symptomatic hyperthyroidism, atezolizumab should be withheld and an anti-thyroid medicinal product such as methimazole or carbimazole should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with 1-2 mg/kg per day of IV methylprednisolone or equivalent should be started. Once symptoms improve, treatment with 1-2 mg/kg per day of oral prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg per day methylprednisolone or equivalent) should be started, and hormone replacement initiated as needed. Once symptoms improve, treatment with 1-2 mg/kg per day of oral prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose >250-500 mg/dL), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-related pancreatitis
Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.
Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2x ULN), or Grade 2 or 3 pancreatitis, and treatment with 1-2 mg/kg IV methylprednisolone or equivalent per day, should be started. Once symptoms improve, follow with 1-2 mg/kg oral prednisone or equivalent per day. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Other immune-related adverse reactions
The following additional clinically significant immune-related adverse reactions have been reported in patients receiving atezolizumab ; myasthenic syndrome/myasthenia gravis, Guillian-Barré syndrome, menigeonacephalitis and myocarditis (see section 4.8).

Treatment with atezolizumab must be permanently discontinued for any grade of immune-related myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome or meningoencephalitis. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg/day of prednisone or equivalent) should be considered.
Patients with signs and symptoms of myocarditis should be closely monitored and referred to a specialist for assessment and treatment without delay. Based on the severity of myocarditis, atezolizumab should be withheld or discontinued, and appropriate treatment instituted (see sections 4.2).

Infusion-related reactions
Severe infusion reactions have occurred in patients in clinical trials of atezolizumab. Infusion should be interrupted or its rate slowed down in patients with mild or moderate infusion reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion reactions (see section 4.2, Table 1 for dose modification guidelines).

Special Populations

Autoimmune disease
Patients with autoimmune disease were excluded from clinical trials with atezolizumab (see section 5.1). In the absence of data, atezolizumab should be used with caution in patients with autoimmune disease, after assessment of the potential risk-benefit.

Severe infections
Patients with severe active infections were excluded from clinical trials with atezolizumab. In the absence of data, atezolizumab should not be used in patients with severe infections within 4 weeks of starting treatment or signs or symptoms of infections within 2 weeks of starting study treatment.

Severe reactions to immune checkpoint inhibitors
In the absence of data, atezolizumab should not be used in patients with severe reactions to immune checkpoint inhibitors.

Live attenuated vaccine
Patients who had administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation were excluded from clinical trials with atezolizumab. Patients must not receive live attenuated influenza vaccine within 4 weeks prior to study treatment initiation or at any time during the treatment, and for 5 months thereafter.

Patient Alert Card

The prescriber must discuss the risks of atezolizumab therapy with the patients and provide them with the Patient Alert Card.

Each patient must be given a Patient Alert Card before they start treatment with atezolizumab. The patients must keep this alert card with them at all times during the treatment and for at least 5 months after their last treatment dose. The card summarises that they are currently receiving atezolizumab, the important side effects for which patients need to seek assistant should they occur, details of the patient's treating oncologist managing their treatment, out of hours contact details and the company contact details.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with atezolizumab.

The use of systemic corticosteroids or other immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and up to 5 months after treatment with atezolizumab.

Pregnancy

There are no data from the use of atezolizumab in pregnant women. Atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab.

Breast-feeding

It is unknown whether atezolizumab is excreted in human milk. No studies have been conducted to assess the

impact of atezolizumab on milk production or its presence in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue atezolizumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies to evaluate the effect of atezolizumab on fertility have not been performed. Thus, the effect of atezolizumab on male and female fertility is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

There are no known effects of atezolizumab on the ability to drive and use machines. However, patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of atezolizumab is based on pooled data in 2,160 patients with metastatic urothelial carcinoma and NSCLC, with supporting data from the cumulative exposure in 6,000 patients across all clinical trials in multiple tumour types. The most common adverse reactions were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), pyrexia (18.3%), rash (18.6%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Table 2 summarises the adverse drug reactions that have been reported in association with the use of atezolizumab during treatment or within 30 days from last dose of treatment.

Tabulated list of adverse reactions

The Adverse Drug Reactions (ADRs) are listed below by MedDRA system organ class (SOC) and categories of frequency. The following categories of frequency have been used: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 Summary of adverse reactions occurring in patients treated with atezolizumab in clinical trials

ADR (MedDRA)	
System Organ Class	Frequency Category
Blood and Lymphatic System Disorders	
Thrombocytopenia	Common
Immune System Disorders	
Hypersensitivity	Common
Hypothyroidism[a]	Common
Hyperthyroidism[b]	Common
Diabetes mellitus[c]	Uncommon
Adrenal insufficiency[d]	Uncommon
Hypophysitis	Rare
Metabolism and Nutrition Disorders	
Decreased appetite	Very Common
Hypokalaemia	Common

Hyponatremia	Common
Nervous System Disorders	
Guillain-Barré syndrome[e]	Uncommon
Noninfective meningitis[f]	Uncommon
Noninfective encephalitis[g]	Rare
Myasthenic syndrome [h]	Rare
Cardiac Disorders	
Myocarditis[h]	Rare
Vascular Disorders	
Hypotension	Common
Respiratory, Thoracic, and Mediastinal Disorders	
Dyspnoea	Very Common
Pneumonitis[i]	Common
Hypoxia	Common
Nasal congestion	Common
Gastrointestinal Disorders	
Nausea	Very Common
Diarrhoea	Very Common
Vomiting	Very Common
Abdominal pain	Common
Dysphagia	Common
Colitis [j]	Common
Lipase increased	Uncommon
Pancreatitis[k]	Uncommon
Amylase increased	Rare
Hepatobiliary Disorders	
AST increased	Common
ALT increased	Common
Hepatitis[l]	Uncommon
Skin and Subcutaneous Tissue Disorders	
Rash[m]	Very Common
Pruritus	Very Common
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	Very Common
Musculoskeletal pain	Common
General Disorders and Administration Site Conditions	
Fatigue	Very Common

Pyrexia	Very Common
Asthenia	Very Common
Chills	Common
Influenza like illness	Common
Infusion related reaction	Common

[a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, myxoedema, thyroiditis, acute thyroiditis, blood thyroid stimulating hormone decreased, abnormal thyroid function test, thyroxine decreased

[b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, myxoedema, thyroiditis, acute thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, abnormal thyroid function test, thyroxine decreased

[c] Includes reports of diabetes mellitus and type 1 diabetes mellitus

[d] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease

[e] Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy

[f] Includes reports of meningitis

[g] Includes reports of encephalitis

[h] The frequency is based on the exposure across all atezolizumab clinical trials.

[i] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis

[j] Includes reports of colitis, autoimmune colitis, ischaemic colitis, microscopic colitis

[k] Includes reports of pancreatitis and acute pancreatitis

[l] Includes reports of autoimmune hepatitis, hepatitis, acute hepatitis

[m] Includes reports of erythema (including multiforme, of the eyelid); rash (including erythematous, maculo-papular, macular, papular, papulosquamous, pruritic, pustular, generalised, toxic, of the eyelid); dermatitis (including acneiform, seborrheic, allergic, bullous, exfoliative); eczema; acne; skin eruption, exfoliation, toxicity, ulcer; palmar-plantar erythrodysaesthesia syndrome; drug eruption folliculitis, furuncle

Description of selected adverse reactions

The data below reflect exposure to atezolizumab for clinically significant adverse reactions in 2,160 patients from five clinical studies in metastatic urothelial carcinoma and NSCLC. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-related pneumonitis
Pneumonitis occurred in 3.1% (68/2,160) of patients who received atezolizumab. Of the 68 patients, one experienced a fatal event. The median time to onset was 3.5 months (range: 3 days to 20.5 months). The median duration was 1.5 months (range: 0 days to 15.1+ months). Pneumonitis led to discontinuation of atezolizumab in 10 (0.5 %) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (34/2,160) of patients receiving atezolizumab.

Immune-related hepatitis
Hepatitis occurred in 0.3% (7/2,160) of patients who received atezolizumab. The median time to onset was 1.1 months (range: 9 days to 7.9 months). The median duration was 1 month (range: 9 days to 1.9+ months). Hepatitis led to discontinuation of atezolizumab in 2 (<0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2,160) of patients receiving atezolizumab.

Immune-related colitis
Colitis occurred in 1.1% (23/2,160) of patients who received atezolizumab. The median time to onset was 4 months (range: 15 days to 15.2 months). The median duration was 1.4 months (range: 3 days to 17.8+ months). Colitis led to discontinuation of atezolizumab in 5 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (10/2,160) of patients receiving atezolizumab.

Immune-related endocrinopathies
Hypothyroidism occurred in 4.7% (101/2,160) of patients who received atezolizumab. The median time to

onset was 5.5 months (range: 15 days to 31.3 months). Hyperthyroidism occurred in 1.7% (36/2,160) of patients who received atezolizumab. The median time to onset was 3.5 months (range: 21 days to 31.3 months). Adrenal insufficiency occurred in 0.3% (7/2,160) of patients who received atezolizumab. The median time to onset was 5.7 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (6/2,160) of patients receiving atezolizumab. Hypophysitis occurred in <0.1% (1/2,160) of patients who received atezolizumab. The time to onset was 13.7 months.
Diabetes mellitus occurred in 0.3% (6/2,160) of patients who received atezolizumab. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of atezolizumab in 1 (<0.1%) patient.

Immune-related meningoencephalitis
Meningitis occurred in 0.1% (3/2,160) of patients who received atezolizumab. The time to onset ranged from 15 to 16 days. All three patients required the use of corticosteroids and discontinued atezolizumab. Encephalitis occurred in <0.1% (2/2,160) of patients. The time to onset was 14 and 16 days. Encephalitis led to the discontinuation of atezolizumab in 1 (<0.1%) patient. Encephalitis requiring the use of corticosteroids occurred in <0.1% (1/2,160) of patients receiving atezolizumab.

Immune-related neuropathies
Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/2,160) of patients who received atezolizumab. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (0+ day to 8.3+ months). Guillain-Barré syndrome led to the discontinuation of atezolizumab in 1 patient (<0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/2,160) of patients receiving atezolizumab.

Myasthenic syndrome/myasthenia gravis occurred in <0.1% (4/6,000) of patients across all atezolizumab clinical trials. The time to onset ranged from 20 days to 4 months. All four patients discontinued atezolizumab. Myasthenic syndrome/myasthenia gravis requiring the use of corticosteroids occurred in <0.1% (3/6,000) of patients receiving atezolizumab.

Immune-related pancreatitis
Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (10/2,160) of patients who received atezolizumab. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 18 days (range: 3 days to 11.2+ months). Pancreatitis requiring the use of corticosteroids occurred in <0.1% (2/2,160) of patients receiving atezolizumab.

Note: + denotes a censored value

4.9 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should 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, monoclonal antibodies. ATC code: not yet assigned.

Mechanism of action

PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in an increased frequency of activated cytotoxic T- cells and decreased tumour growth.

Clinical efficacy and safety

PD-L1 expression by IHC

Immunohistochemistry (IHC) was assessed by a central laboratory and was performed on tumour cells (TC) and tumour-infiltrating immune cells (IC). The test detects the presence of any discernible PD-L1 staining of any intensity. Scoring for tumour cells was defined as TC0 (<1%), TC1 (≥ 1% and < 5%), TC2 (≥ 5% and < 50%), and TC3 (≥ 50%). Scoring for tumour-infiltrating immune cells was defined as IC0 (< 1%), IC1 (≥ 1% and < 5%), IC2 (≥ 5% and < 10%) and IC3 (≥ 10%).

Duration of treatment

For previously treated patients in the pivotal studies treatment with atezolizumab was permitted until loss of clinical benefit as defined by the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcaemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilised by protocol-allowed medical interventions prior to repeat dosing
- Evidence of clinical benefit as assessed by the investigator.

Urothelial Carcinoma

A phase II, multi-centre, international, two-cohort, single-arm clinical trial, GO29293 (IMvigor210), was conducted in patients with locally advanced or metastatic urothelial carcinoma (also known as urothelial bladder cancer). In Cohort 2, 311 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with atezolizumab. This study excluded patients who had: an ECOG status > 1, a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications.

Atezolizumab was given as a fixed dose of 1,200 mg by intravenous infusion on Day 1 of a 21-day cycle until loss of clinical benefit as assessed by the investigator. Tumour response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumours (RECIST v1.1) and duration of response (DoR).

In this cohort, the median age was 66 years, 78% were male, 91% patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG score of 1 and 35% of patients had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty one percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumour specimens were evaluated prospectively using the Ventana PD-L1 (SP142) assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. In the primary analysis (median follow-up time of 7.1 months), the study met its co-primary endpoints in all subgroups (IC2/3, IC1/2/3, and all comers), demonstrating significant improvements of ORR per IRF-RECIST v1.1 and per investigator-modified RECIST compared to a historical chemotherapy control response rate of 10%.

An updated efficacy analysis (median follow-up of 21.1 months) is summarised in Table 3.

Table 3 Summary of Efficacy from GO29293 Cohort 2

Efficacy Endpoints	IC2/3	IC0/1	All Comers
ORR (IRF-Assessed RECIST v1.1)	N=100	N=210	N=310
Number of responders (%)	28 (28.0%)	21 (10.0%)	49 (15.8 %)
95% CI	19.5, 37.9	6.3, 14.9	11.9, 20.4
DoR (IRF-Assessed; RECIST v1.1)	n=28	n=21	n=49
Patients with Event (%)	9 (32.1%)	8 (38.1%)	17 (34.7%)
Median (months)	NE	NE	NE
95% CI	4.2, 22.6*	2.1*, 19.5*	2.1*, 22.6*
PFS (IRF-Assessed; RECIST v1.1)			
Patients with Event (%)	80 (80.0%)	194 (92.4%)	274 (88.4%)
Median (months)	2.1	2.1	2.1
95% CI	2.1, 4.2	2.0, 2.1	2.1, 2.1
OS			
Patients with Event (%)	58 (58.0%)	168 (80.0%)	226 (72.9%)
Median (months)	11.9	6.7	7.9
95% CI	9.0, NE	5.4, 8.0	6.7, 9.3
12-month rate (%)	49.9	30.6	36.9
95% CI	40.0, 59.9	24.3, 37.0	31.4, 42.3

CI=confidence interval; DOR=duration of objective response; IC= tumour-infiltrating immune cells; IRF=independent review facility; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.

In the subgroup of 145 patients who had only one prior line of therapy regardless of its setting (neoadjuvant, adjuvant, or metastatic), the objective response rate (IRF-Assessed RECIST v1.1) is summarised in Table 4. The median OS was 8.8 months (95%CI; 6.7, 11.4) in all comers and 11.4 months (95%CI; 7.6, NE) in the IC 2/3 subgroup.

Table 4 ORR by IC subgroup (2L patients, n=145)

IC Subgroup	ORR (%) and 95% CI	CR (%)	PR (%)
IC 2/3 (n=45)	26.7 (14.6, 41.9)	7 (15.6%)	5 (11.1%)
IC 0/1 (n=100)	12.0 (6.4, 20.0)	3 (3.0%)	9 (9.0%)
All comers (n=145)	16.6 (10.9, 23.6)	10 (6.9%)	14 (9.7%)

Immunogenicity

In study GO29293, 41.9% of patients tested positive for anti-atezolizumab antibodies at one or more post-dose

time points. Overall, these antibodies appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety.

5.2 Pharmacokinetic properties

The pharmacokinetics of atezolizumab has been characterised in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg every 3 weeks including the fixed dose 1,200 mg. Exposure to atezolizumab increased dose proportionally over the dose range: 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1-20 mg/kg with a linear two-compartment disposition model with first-order elimination. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve, maximum concentration and trough concentration was 1.91, 1.46 and 2.75-fold, respectively.

Based on an analysis of exposure, safety and efficacy data, the following factors have no clinically relevant effect: age (21-89 years), body weight, gender, positive ATA status, albumin levels, tumour burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

Absorption

Atezolizumab is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution is 3.28 L and volume at steady-state is 6.91 L in the typical patient.

Biotransformation

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life is 27 days.

Elderly people

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n=274), patients between 65-75 years (n=152) and patients > 75 years (n = 46) (see section 4.2).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of atezolizumab in children.

Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=208) or, moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2;

n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n=8) (see section 4.2).

Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5x ULN and any AST, n= 71) and normal hepatic function (bilirubin and AST≤ ULN, n= 401). No data are available in patients with either moderate or severe hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 4.2).

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of atezolizumab.

Mutagenicity

Mutagenicity studies have not been performed to establish the mutagenic potential of atezolizumab.

Fertility

No fertility studies have been conducted with atezolizumab; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Atezolizumab had an effect on menstrual cycles in all female monkeys in the 50 mg/kg dose group characterised by an irregular cycle pattern during the dosing phase and correlated with the lack of fresh corpora lutea in the ovaries at the terminal necropsy; this effect was reversible during the dose-free recovery period.
There was no effect on the male reproductive organs.

Teratogenicity

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death. Administration of atezolizumab is expected to have an adverse reaction on pregnancy and poses a risk to the human fetus, including embryo lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Glacial acetic acid
Sucrose
Polysorbate 20
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C and 8 hours at ambient temperature (≤ 30 °C) from the time of preparation.
From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Keep the vial in the outer carton in order to protect from light.

Do not freeze. Do not shake.

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

6.5 Nature and contents of container

Vial (Type I glass) with a stopper (butyl rubber) containing 20 mL of solution.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Atezolizumab does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique.

Instructions for dilution

Twenty mL of atezolizumab concentrate should be withdrawn from the vial and diluted into a 250 mL PVC, polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, one mL of solution should contain approximately 4.4 mg of atezolizumab (1,200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately (see section 6.3).

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

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

7. SCIENTIFIC OPINION HOLDER

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8. EAMS NUMBER

00031/0001

9. DATE OF SCIENTIFIC OPINION

20/01/2017

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