Medicines & Healthcare products Regulatory Agency

MHRA

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

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and is to be used in combination with (an)other medicine(s) prescribed outside the licence. The information is provided to assist physicians in prescribing medicines used outside the licence. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the combination therapy in this new promising indication. As such, this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such an indication, nor should it be regarded as an authorisation to sell or supply a medicine for such an indication. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated. For other updates of the safety information, please refer to the product information of the combination products on the electronic Medicines Compendium (eMC) website: https://www.medicines.org.uk/emc.

Contact information regarding queries on using 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 20 mL vial of concentrate contains 1,200 mg atezolizumab*.

After dilution (see section 6.6), one mL of solution contains approximately 4.4 mg of atezolizumab.

*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.

Clear, colourless to slightly yellowish liquid.

4. CLINICAL PARTICULARS

4.1 EAMS Therapeutic indication

Atezolizumab, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma who have received no prior systemic therapy (see section 5.1).

Healthcare professionals are advised to consult the Summary of Product Characteristics (SmPC) of the combined product(s) for further information on administration, safety aspects and pharmaceutical particulars.

4.2 Posology and method of administration

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer. Please also refer to the SmPC for bevacizumab.

Posology

The recommended dose of atezolizumab is 1,200 mg followed by 15 mg/kg of body weight of bevacizumab, administered by intravenous infusion 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. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

Dose modifications during treatment
Dose reductions of atezolizumab are not recommended.

Dose delay or discontinuation (see also sections 4.4 and 4.8)

Table 1: Dose modification advice for atezolizumab

Immune related 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 prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to >3x to ≤10x ULN *or* If AST/ALT is >1 to ≤3x ULN at baseline and increases to >5x to ≤10x ULN *or* If AST/ALT is >3x to ≤5x ULN at baseline and increases to >8x to ≤10x ULN	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 prednisone or equivalent per day
	If AST/ALT increases to >10x ULN or total bilirubin increases to >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 prednisone or 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 anti-thyroid medicinal product 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 ≤ 10 mg 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 ≤ 10 mg 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 mg/dL or 13.9 mmol/L)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is 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 prednisone or equivalent per day
	Grade 4	Permanently discontinue atezolizumab
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue atezolizumab

Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold atezolizumab Treatment 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 prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab
Myocarditis	Grade 2	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 ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	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 prednisone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue atezolizumab
Myositis	Grade 2 or 3	Withhold atezolizumab
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue atezolizumab
Other immune-related adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)

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

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
Based on a population pharmacokinetic analysis, no dose adjustment of atezolizumab is required in patients ≥ 65 years of age (see sections 4.8 and 5.1).

Renal impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. Atezolizumab has not been studied in patients with severe hepatic impairment (see section 5.2).

Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2
Patients with ECOG performance status ≥ 2 were excluded from the clinical trial in HCC (see sections 4.4 and 5.1).

Method of administration

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

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

For instructions on dilution and handling of atezolizumab before administration, see section 6.6.

Please refer to the SmPC of bevacizumab for instructions regarding the method of administration of this product.

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

Traceability

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

Immune-related adverse reactions

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 have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, thorough 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 systemic corticosteroid use, administration of other systemic immunosuppressants may 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 reactions, 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 to 2 mg/kg/day prednisone or equivalent 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 prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-related hepatitis in patients with HCC

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.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) 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 ALT or AST increases to > 3 to 10 x ULN from normal limits at baseline, or > 5 to10 x ULN from > ULN to 3 x ULN at baseline, or > 8 to10 x ULN from > 3 ULN to 5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves 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 prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x 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 to 2 mg/kg/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent 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 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 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 intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms

improve, treatment with 1 to 2 mg/kg/day of 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 ≤ 10 mg prednisone or equivalent per day and the 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/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg/day of 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 ≤ 10 mg 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 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-related meningoencephalitis

Meningoencephalitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow.

Immune-related neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy.

Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg/day of prednisone or equivalent) should be considered.

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 (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. 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 prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Immune-related myocarditis

Myocarditis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis.

Treatment with atezolizumab should be withheld for Grade 2 myocarditis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 myocarditis.

Immune-related nephritis

Nephritis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for changes in renal function.

Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.

Immune-related myositis

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

Treatment with atezolizumab should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. 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 should be permanently discontinued for Grade 4 or grade 3 recurrent

myositis, or when unable to reduce the corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Infusion-related reactions

Infusion-related reactions have been observed with atezolizumab (see section 4.8).

The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Patients excluded from clinical trial IMbrave 150

Patients with the following conditions were excluded from IMbrave 150: a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, significant cardiovascular disease, known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC, untreated or incompletely treated oesophageal and/or gastric varices with bleeding or high risk for bleeding, prior bleeding event due to oesophageal and/or gastric varices within last 6 months, moderate or severe ascites, history of hepatic encephalopathy, co-infection of HBV and HCV, Child-Pugh class B and C, and patients with inadequate hematologic and end-organ function. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry were also excluded.

Patients with an active Hepatitis B virus infection were excluded if they did not have HBV DNA □□500 IU/mL obtained within 28 days prior to initiation of study treatment, and anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry.

In the absence of data, atezolizumab should be used with caution in these populations, after careful consideration of the potential benefit/risk on an individual basis

Patient alert card

All prescribers of atezolizumab must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of atezolizumab therapy with the patient. The patient will be provided with the patient alert card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

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

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune related adverse reactions after starting atezolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no data from the use of atezolizumab in pregnant women. No developmental and reproductive studies were conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD L1/PD 1 pathway in murine pregnancy models can lead to immune related rejection of the developing foetus resulting in foetal death (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of atezolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human immunoglobulins G1 (IgG1) are known to cross the placental barrier and atezolizumab is an IgG1; therefore, atezolizumab has the potential to be transmitted from the mother to the developing foetus.

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. Atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards. A risk to the newborns/infants cannot be excluded. 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

No clinical data are available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab; however, based on the 26 week repeat dose toxicity study, atezolizumab had an effect on menstrual cycles at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible (see section 5.3). There were no effects on the male reproductive organs.

4.7 Effects on ability to drive and use machines

Atezolizumab has minor influence on the ability to drive and use machines. 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

For the safety of atezolizumab, please refer to the SPC of Tecentriq®(atezolizumab).
For the safety of bevacizumab, please refer to the SPC of Avastin®(bevacizumab).

Overall, the nature and incidence of Adverse Drug Reactions (ADRs) observed in patients treated atezolizumab+bevacizumab is consistent with the known safety profile of the individual medicinal products. The most frequently reported ADRs were previously known ADRs of either of the individual treatments, except for the new observed ADR of peripheral oedema.

The safety of atezolizumab given in combination with bevacizumab for the treatment of HCC has been evaluated in 493 patients with locally advanced or metastatic HCC who had not received prior systemic treatment: 329 in the pivotal study IMbrave 150 and 164 in the supportive phase 1b study GO30140. The most common (≥ 20%) adverse reactions were: hypertension (26.2%), proteinuria (23.9%), fatigue (21.9%) and decreased appetite (20.7%). The most common serious adverse reactions were: pyrexia (2.6%), oesophageal varices haemorrhage (2.0%), and gastrointestinal haemorrhage (1.8%).

Table 2 summarises the ADRs associated with the combination of atezolizumab and bevacizumab with by MedDRA system organ class (SOC) and frequency.

Table 2: Summary of Adverse Drug Reactions reported in ≥10% of patients in studies IMbrave 150 and GO30140

MedDRA System Organ Class MedDRA Preferred Term	Frequency (%)
General disorders and administration site conditions	
Fatigue	22
Pyrexia	18
Oedema peripheral	10
Gastrointestinal disorders	
Diarrhoea	19
Abdominal pain	14
Constipation	14
Nausea	12
Respiratory, thoracic and mediastinal disorders	
Cough	12
Epistaxis	11
Musculoskeletal and connective tissue disorders	
Arthralgia	11
Metabolism and nutrition disorders	
Decreased appetite	21
Skin and subcutaneous tissue disorders	
Pruritus	18
Rash	16
Investigations	
Aspartate aminotransferase increased	17
Alanine aminotransferase increased	12
Blood bilirubin increased	12
Platelet count decreased	12
Renal and urinary disorders	
Proteinuria	24
Vascular disorders	
Hypertension	26

Description of selected adverse reactions

The following adverse reactions associated with the use of atezolizumab monotherapy occurred more frequently in patients who received atezolizumab + bevacizumab:
- Hypothyroidism occurred in 9.9% (49/493) of patients who received atezolizumab + bevacizumab
- Hyperthyroidism occurred in 3.2% (16/493) of patients who received atezolizumab + bevacizumab
- Infusion-related reactions occurred in 8.7% (43/493) of patients who received atezolizumab + bevacizumab.

Immunogenicity
Anti-drug-antibody incidence rates ranged between 24% to 38% in studies IMbrave150 and GO30140 and are generally in line with the range of treatment-emergent ADA incidence rates observed across atezolizumab studies (13.1 % to 36.4%). Overall, ADA status appeared to have no clinically relevant impact on safety.
No data are available to allow conclusions to be drawn on possible effects of neutralising antibodies.

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: L01XC32

Mechanism of action

Programmed death ligand 1 (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.

Clinical efficacy and safety

Duration of treatment

Treatment with atezolizumab until loss of clinical benefit was permitted 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

IMbrave150 (YO40245): Randomised phase III trial in patients with unresectable HCC who have not received prior systemic therapy, in combination with bevacizumab

A phase III, randomised, multi-center, international, open-label study, IMbrave150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab, in adult patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment and with a disease that was not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies. A total of 501 patients were randomised (2:1) to receive either atezolizumab (1,200 mg) and 15 mg/kg of bevacizumab every 3 weeks administered by intravenous infusion, or sorafenib 400 mg orally twice per day. Randomisation was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline α-fetoprotein (AFP) (<400 vs. ≥400 ng/mL) and ECOG performance status (0 vs. 1). Patients in both arms received treatment until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either atezolizumab or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults who were Child-Pugh A, ECOG 0/1 and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation; untreated or corticosteroid-dependent brain metastases. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic

spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorised as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The key efficacy results are summarised in Table 3. Kaplan-Meier curves for OS and PFS are presented in Figures 1 and 2.

Table 3: Summary of efficacy (IMbrave150)

Key efficacy endpoints	**Atezolizumab +bevacizumab**		**Sorafenib**	
OS	n=336		n=165	
No. of deaths (%)	96 (28.6%)		65 (39.4%)	
Median time to event (months)	NE		13.2	
95% CI	(NE, NE)		(10.4, NE)	
Stratified hazard ratio‡ (95% CI)	0.58 (0.42, 0.79)			
p-value[1]	0.0006			
6-month OS (%)	84.8%		72.3%	
	RECIST v1.1		**HCC mRECIST**	
	Atezolizumab + bevacizumab	Sorafenib	Atezolizumab + bevacizumab	Sorafenib
IRF-assessed PFS	n=336	n=165	n=336	n=165
No. of events (%)	197 (58.6%)	109 (66.1%)	199 (59.2%)	111 (67.3%)
Median duration of PFS (months)	6.8	4.3	6.8	4.2
95% CI	(5.8, 8.3)	(4.0, 5.6)	(5.7, 7.7)	(4.0, 5.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.47, 0.76)		0.59 (0.46, 0.74)	
p-value[1]	<0.0001		N/A	
6-month PFS	54.5%	37.2%	54.3%	36.4%
IRF-assessed ORR	n=326	n=159	n=325	n=158
No. of confirmed responders (%)	89 (27.3%)	19 (11.9%)	108 (33.2%)	21 (13.3%)
95% CI	(22.5, 32.5)	(7.4, 18.0)	(28.1, 38.6)	(8.4, 19.6)
p-value[2]	<0.0001		<0.0001	
No. of complete responses (%)	18 (5.5%)	0	33 (10.2%)	3 (1.9%)
No. of partial responses (%)	71 (21.8%)	19 (11.9%)	75 (23.1%)	18 (11.4%)
No. of stable disease (%)	151 (46.3%)	69 (43.4)	127 (39.1%)	66 (41.8%)
IRF-assessed DOR	n=89	n=19	n=108	n=21
Median in months	NE	6.3	NE	6.3
95% CI	(NE, NE)	(4.7, NE)	(NE, NE)	(4.9, NE)
6-month DOR (%)	87.6%	59.1%	82.3%	62.5%

‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)

1. Based on two-sided stratified log-rank test

2. Based on two-sided Cochran-Mantel-Haenszel test

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma ; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable; N/A=not applicable

Figure 1*:* Kaplan-Meier curve for OS in the ITT population (IMbrave150)

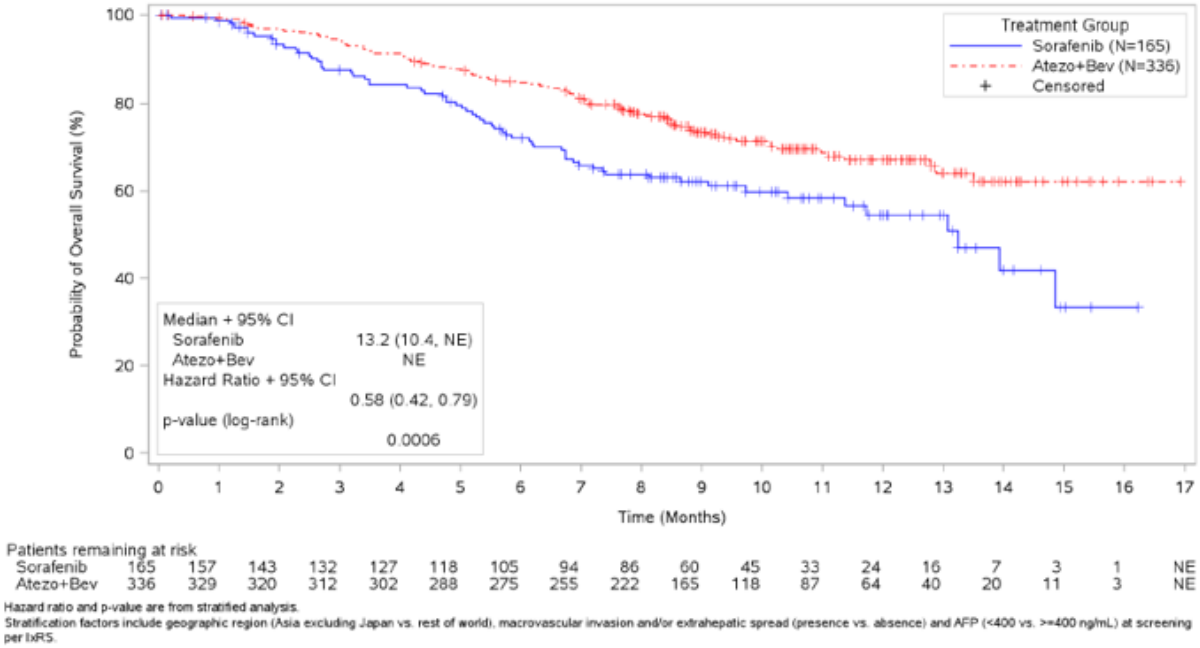
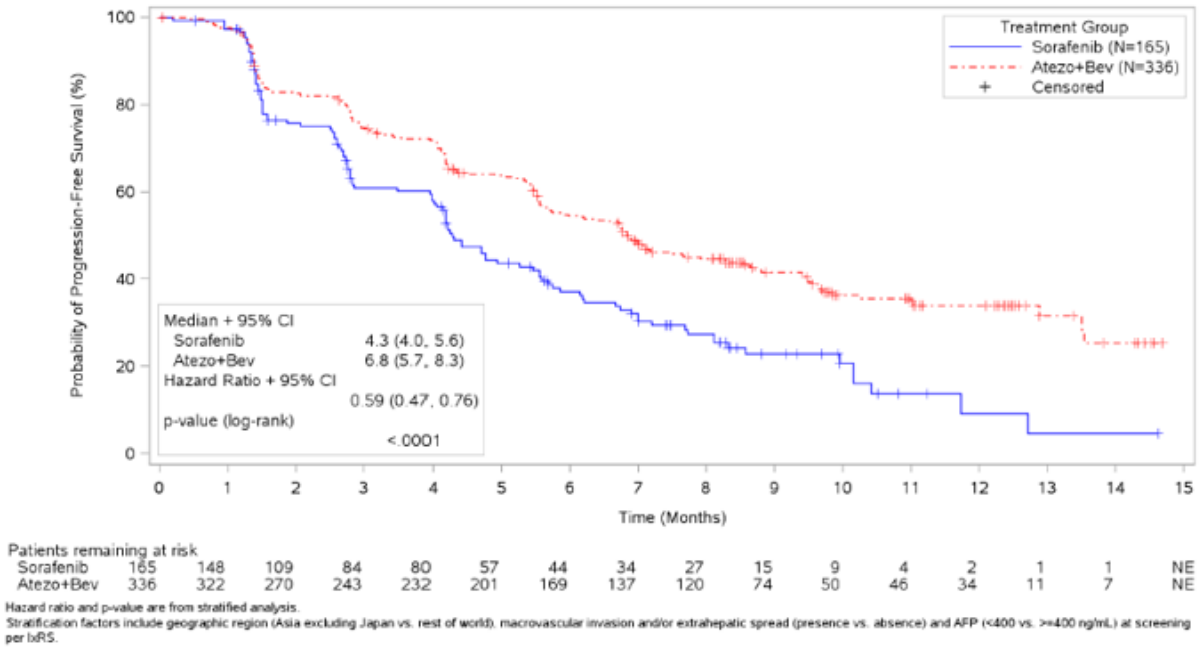


Figure 2: Kaplan-Meier curve for IRF-PFS per RECIST v1.1 in the ITT population (IMbrave150)



The study evaluated patient-reported outcomes using the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires. Time to deterioration (TTD) of patient-reported physical functioning, role functioning, and global health status/quality of life (GHS/QoL) on the EORTC QLQ-C30 were pre-specified secondary endpoints. TTD was defined as the time from randomization to the first deterioration (decrease from baseline of ≥10 points) maintained for two consecutive assessments, or one assessment followed by death from any

cause within 3 weeks. Compared with sorafenib, treatment with atezolizumab and bevacizumab delayed deterioration of patient-reported physical functioning (median TTD: 13.1 vs. 4.9 months; HR 0.53, 95% CI 0.39, 0.73), role functioning (median TTD: 9.1 vs. 3.6 months; HR 0.62, 95% CI 0.46, 0.84), and GHS/QoL (median TTD: 11.2 vs. 3.6 months; HR 0.63, 95% CI 0.46, 0.85).

5.2 Pharmacokinetic properties

Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg to 20 mg/kg including the fixed dose 1,200 mg administered every 3 weeks. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 to 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.

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.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Elderly
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 or adolescents.

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 (estimated glomerular filtration rate [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). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

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 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) . No data are available in patients with severe hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 4.2). The effect of severe hepatic impairment (bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

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. However, monoclonal antibodies are not expected to alter DNA or chromosomes.

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. Weekly administration of atezolizumab to female monkeys at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries which were reversible. 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 immune-related rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo-foetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at ≤ 30 °C and for up to 30 days at 2 °C to 8 °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 and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C) unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

Do not freeze.

Keep the vial in the outer 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 with a butyl rubber stopper and an aluminium seal with a plastic aqua flip-off cap containing 20 mL of concentrate solution for infusion.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Atezolizumab does not contain any antimicrobial preservative or bacteriostatic agents and should be prepared by a healthcare professional using aseptic technique to ensure the sterility of prepared solutions.

Aseptic preparation, handling and storage
Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions.

Do not shake.

Instructions for dilution

Twenty mL of atezolizumab concentrate should be withdrawn from the vial and diluted into a 250 mL polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE) or polypropylene (PP) 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 discolouration are observed, the solution should not be used.

No incompatibilities have been observed between atezolizumab and intravenous bags with product-contacting surfaces of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

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

Disposal

The release of atezolizumab in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

00031/0012

9. DATE OF SCIENTIFIC OPINION

18 June 2020

Additional information:

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm patient eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.hcceams@roche.com

A Physician Agreement and Safety Data Exchange agreement will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing haematologist/oncologist will also be provided with a physician pack containing all the relevant documents

needed, including the adverse events reporting form needed to manage patients receiving atezolizumab under the EAMS.

Contact information

Contact details for reporting Adverse Events/Special Situations/Pregnancies:

SAE Email Address: welwyn.uk_dsc@roche.com

SAE Facsimile Transmission: +44 1707 367582

SAE TELEPHONE CONTACT: +44 1707 367554

Name: UK Drug Safety Centre

Contact email for the EAMS programme (excluding AE reporting):

welwyn.hcceams@roche.com

Contact Details for Medical Information

Roche Medical Information on 0800 328 1629 or email medinfo.uk@roche.com