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 and 'off label' medicines 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 medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and is to be used in combination with another medicine prescribed off-label. The information is provided to assist the doctor in prescribing unlicensed medicines. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of this promising new medicine used in combination therapy. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor 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 product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

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

For further updates of the safety information, please refer to the product information of Tecentriq®(atezolizumab) on the EMA website": https://www.ema.europa.eu/documents/product-information/tecentriq-epar-product-information_en.pdf

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

Each 20 mL vial of concentrate contains 1,200 mg atezolizumab*.

After dilution (see section 6.6), one mL of solution contains approximately 3.2 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 indications

Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

4.2 Posology and method of administration

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer.
Patients with previously untreated TNBC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology

Please also refer to the full prescribing information for the combination product (see also section 5.1).
The **recommended dose of atezolizumab is 840 mg** administered by intravenous infusion **(see section 6.6)**, followed by 100 mg/m^2 nab-paclitaxel. For each 28-day cycle, atezolizumab is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8, and 15.

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

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 the appropriate 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: Atezolizumab dose modification advice for specified adverse drug reactions

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	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 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: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x 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 antithyroid 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 and 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
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.).

In study IMpassion130 on the treatment combination, dose modifications for nab-paclitaxel were recommended for haematologic and neurological toxicities (see table 2).

Table 2: Nab-paclitaxel dose modification advice

	Occurrence	**Weekly nab-paclitaxel dose modification**
Neurological toxicity		
Grade 3-4 peripheral neuropathy	First	Withhold treatment until resolves to Grade ≤ 1, then resume treatment at 75 mg/m^2
	Second	Withhold treatment until

		peripheral neuropathy resolves to Grade ≤ 1, then resume treatment at 50 mg/m^2
	Third	Discontinue treatment
Haematologic toxicity		
Neutropenic fever (nadir ANC < 500/μL with fever > 38°C) *or* Delay of first administration of nab-paclitaxel in a cycle by > 7 days for nadir ANC < 1500/μL	First	Reduce dose to 75mg/m^2
	Second	Reduce dose to 50mg/m^2
	Third	Discontinue treatment
Nadir ANC < 500/μL for > 7 days Nadir platelet count < 50,000/μL	First	Reduce dose to 75mg/m^2
	Second	Discontinue treatment

Patients treated with atezolizumab must be given the Patient Alert Card and be informed about the risks of atezolizumab (see also package leaflet).

Patients should also be informed about the risks of nab-paclitaxel. Please refer to the SPC and PIL of this medicine for detailed information on dose modification, contraindications, precautions and adverse reactions.

Special populations

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

Elderly
There is evidence of both increased efficacy and higher rates of adverse reactions to atezolizumab and chemotherapy in patients ≥65 years of age including adverse reactions leading to withdrawal of treatment. 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 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 hepatic impairment. Atezolizumab has not been studied in patients with moderate or 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 (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 SPC of nab-paclitaxel 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

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.

Neutropenia and peripheral neuropathies occurring during treatment with atezolizumab may be reversible with interruptions of atezolizumab and/or nab-paclitaxel (see sections 4.2 and 4.8).

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

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 Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) 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 for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 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 antithyroid 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, have 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. 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 2 mg/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.

Infusion-related reactions

Infusion related reactions have been observed in clinical trials 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 IMpassion130

Patients with the following conditions were excluded from the clinical trial: age <18 years; a baseline performance status ≥ 2; a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection; significant cardiovascular disease 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 or (neo)adjuvant chemotherapy within 12 months prior to study entry, were also excluded.

In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Patients were not typed for BRCA mutations in the IMpassion130 study.

Health care professionals are advised to consult the SPC of nab-paclitaxel for the specific precautions and contraindications of this medicine.

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 fetus resulting in fetal 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 fetal 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 fetus.

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 as monotherapy, please refer to the SPC of Tecentriq®(atezolizumab).

For the safety of nab-paclitaxel as monotherapy, please refer to the SPC of Abraxane® (paclitaxel albumin)

In study IMpassion130, the regimen of atezolizumab and nab-paclitaxel induced a higher incidence of grade 3 – 5 adverse events, serious adverse events, immune-related adverse events, and adverse events leading to interruption or discontinuation of atezolizumab or nab-paclitaxel or dose modification/ interruption of nab-paclitaxel. Immune-related adverse events account for about 1/3 of the adverse events leading to interruption or withdrawal of atezolizumab. The adverse event profile combines the immune-related reactions of atezolizumab with the chemotherapy toxicities of nab-paclitaxel.

The safety of atezolizumab given in combination with nab-paclitaxel is based on data in 452 patients with unresectable locally advanced or metastatic TNBC. The most common (≥ 20%) adverse reactions were: alopecia (56.4%), fatigue (46.7%), nausea (46%), peripheral neuropathies (42.5%), rash (34%), diarrhoea (32.5%), neutropenia (32.1%), anaemia (27.7%), constipation (25%), headache (23.2%), cough (24.8%), decreased appetite (20.1%).

Tabulated list of adverse reactions

The Adverse Drug Reactions (ADRs) are listed below by MedDRA system organ class (SOC). Table 3 summarises the ADRs associated with the combination of atezolizumab and nab-paclitaxel that were more frequent than with both monotherapies.

Table 3: Summary of ADRs in study IMpassion130 that were more frequent (≥5%) with the combination than both monotherapies

Adverse event	**Atezolizumab + Nab-Paclitaxel** (N=452)	**Placebo + Nab-paclitaxel** (N=438)	**Atezolizumab monotherapy†** (N=3178)
Blood and lymphatic system disorders			
Neutropenia[a]	32%	26%	*No reports*
Endocrine disorders			
Hypothyroidism[b]	17%	3%	5%
Gastrointestinal Disorders			
Nausea	46%	38%	24%
Skin and Subcutaneous Tissue Disorders			
Rash[c]	34%	26%	20%

† AEs Reported in patients treated with atezolizumab monotherapy across all clinical trials
[a] Includes reports of neutrophil count decreased, febrile neutropenia, neutropenic sepsis.
[b] Includes reports of blood thyroid stimulating hormone increased, autoimmune thyroiditis, thyroiditis, blood thyroid stimulating hormone decreased, goitre, thyroid function test abnormal, thyroxine decreased, thyroxine free increased.

[c] Includes reports of rash, rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, dermatitis, rash erythematous, rash macular, rash papular, skin ulcer, folliculitis, skin exfoliation, erythema multiforme, rash pustular, dermatitis bullous, acne, furuncle, palmar-plantar erythrodysaesthesia syndrome, seborrhoeic dermatitis, dermatitis allergic, drug eruption, rash generalised, erythema of eyelid, skin toxicity, toxic epidermal necrolysis, toxic skin eruption, dermatitis exfoliative, exfoliative rash, eyelid rash, fixed eruption, generalised erythema, rash papulosquamous, rash vesicular

Description of selected adverse reactions in study IMpassion130.

For information on significant adverse reactions of atezolizumab as monotherapy, please refer to the SPC of Tecentriq ® (atezolizumab). The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Neutropenia

A total of 32.1% (145/452) patients in the atezolizumab + nab-paclitaxel arm experienced neutropenia, including 39.4% (41/104) in the patients ≥65 years of age. The median time to first onset was 0.72 months, and 0.49 months in patients ≥65 years of age. 6.9% of patients reporting neutropenia had to delay atezolizumab and 0.2% of patients had to discontinue atezolizumab.

Table 4: Summary of Neutropenia in study IMpassion130

	Grade	Atezolizumab + nab-paclitaxel (n=452)	Placebo + nab-paclitaxel (n=438)
Overall	Any grade	32%	26%
	1-2	19%	14%
	3-4	13%	12%

Peripheral neuropathies

A total of 42.5% (192/452) patients in the atezolizumab + nab-paclitaxel arm experienced peripheral neuropathies, including 53.8% (56/104) in the patients ≥65 years of age. The median time to first onset was 2.55 months, and 2.43 months in patients ≥65 years of age. 1.5% of patients reporting peripheral neuropathies had to delay atezolizumab and 1.3% of patients had to discontinue atezolizumab. Although peripheral neuropathy was not noted as an adverse drug reaction with atezolizumab monotherapy, it has been identified as an adverse drug reaction with atezolizumab in combination with chemotherapy.

Table 5: Summary of peripheral neuropathies in study IMpassion130

	Grade	Atezolizumab + nab-paclitaxel (n=452)	Placebo + nab-paclitaxel (n=438)
Overall	Any grade	42%	39%
	1-2	33%	34%
	3-4	9%	5%

Immunogenicity
In study IMpassion130, the treatment-emergent anti-atezolizumab antibodies (ADAs) rate was 13%. Overall, ADA positivity appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety.

No data are available to allow conclusions to be drawn on any possible effect 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: L01XC

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 anti-tumour 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 anti-tumour 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

IMpassion130 (WO29522): Randomised phase III trial in locally advanced or metastatic TNBC patients previously untreated for metastatic disease

A phase III, double-blind, two-arm, multi-centre international, randomised, placebo-controlled study, IMpassion130, was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. Tumour assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour-infiltrating immune cells (IC). Patients were randomised to receive atezolizumab 840 mg or placebo by intravenous infusions on days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via intravenous infusion on days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity.

Most patients were women (99.6%), 67.5% were white and 17.8% Asian. The median age was 55 years (range: 20-86). Baseline ECOG performance status was 0 (58.4%) or 1 (41.3%). Overall, 41% of enrolled patients had PD-L1 expression ≥1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting.

The co-primary efficacy endpoints included investigator-assessed progression free survival (PFS) in the ITT population and in patients with PD-L1 expression ≥ 1% per RECIST v1.1 as well as overall survival (OS) in the ITT population and in patients with PD-L1 expression ≥ 1%. Secondary efficacy endpoints included objective response rate (ORR) and duration of response (DOR) per RECIST v1.1. At the time of the primary analysis, the median follow-up time was 12.9 months. The median number of treatment cycles was 7 for atezolizumab and 6 for nab-paclitaxel in each treatment arm.

The key efficacy results for patients with PD-L1 expression ≥ 1% are summarized in Table 6 with Kaplan-Meier curves for PFS and OS in Figures 1 and 2.

Table 6: Summary of efficacy in patients with PD-L1 expression ≥1% (IMpassion130)

Key efficacy endpoints	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
Investigator-assessed PFS (RECIST v1.1)	n=185	n=184
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0

95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
12-month PFS (%)	29.1	16.4
Key efficacy endpoints	**Atezolizumab + nab-paclitaxel**	**Placebo + nab-paclitaxel**
1-year OS rate[2]	n=185	n=184
No. of events (%)	44 (23.8%)	62 (33.7%)
KM-Estimate for Event-free rate (%)	75.4%	64.0%
95% CI for KM-Estimate	(69.0, 81.7)	(56.8, 71.3)
Investigator-assessed ORR (RECIST 1.1)	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)
Unstratified hazard ratio (95% CI)	0.60 (0.43, 0.87)	

1. Based on the stratified log-rank test.
2. OS comparisons between treatment arms in patients with PD-L1 expression ≥1% were not formally tested, as per the pre-specified analysis hierarchy.

‡ Stratified by presence of liver metastases, and by prior taxane treatment.
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival, NE=not estimable; KM= Kaplan-Meier

The treatment effect on PFS was broadly consistent across clinical subgroups but notably more effective in patients >65 years, those without prior taxane or anthracycline or (neo)adjuvant chemotherapy, and those with nodal only disease or locally advanced unresectable disease. There was no evidence of efficacy in patients with brain metastases, although the number of patients treated was small; the median PFS was 2.2 months in the atezolizumab+nab-paclitaxel arm (n=15) compared to 5.6 months in the placebo+nab-paclitaxel arm (n=11), (HR 1.40; 95%CI 0.57, 3.44).

Figure 1: Kaplan-Meier Curve for Progression Free Survival in patients with PD-L1 expression ≥ 1% (IMpassion130)

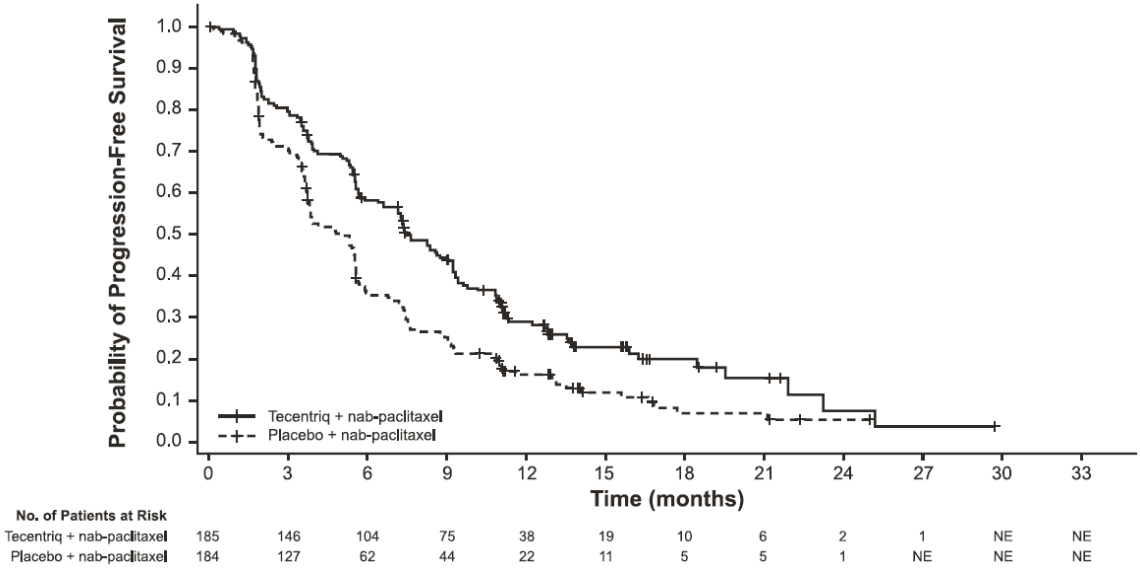
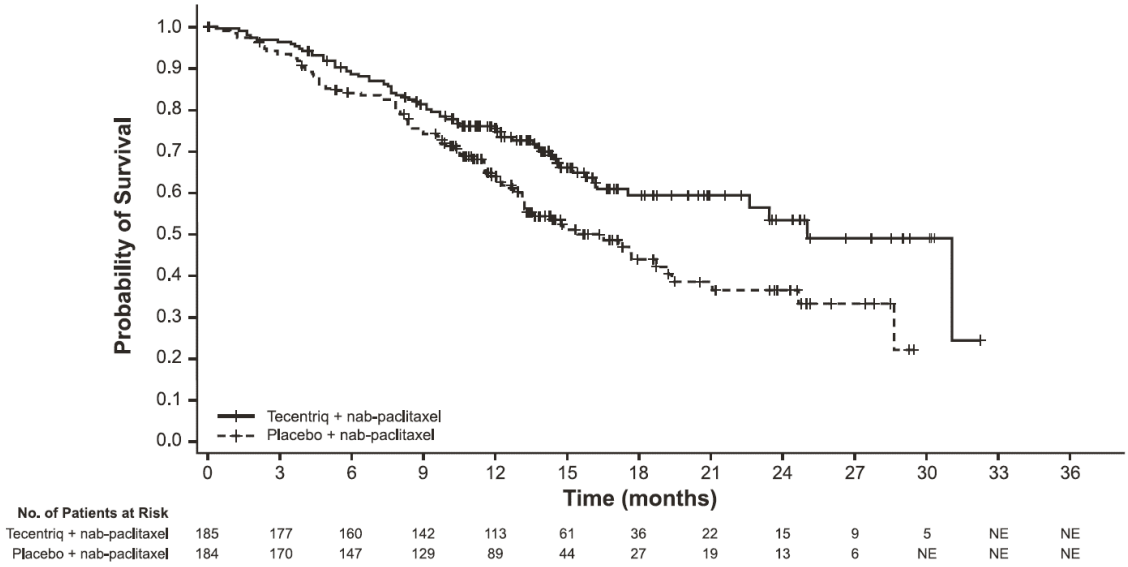


Figure 2: Kaplan-Meier Curve for Overall Survival in patients with PD-L1 expression ≥ 1% (IMpassion130)



Patient-reported endpoints indicate there is no acceleration in the decline of Global Health status (a sustained > 10-point decline from baseline mean score).

5.2 Pharmacokinetic properties

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 to 20 mg/kg with a linear two-compartment disposition model with first-order elimination. The pharmacokinetic properties of atezolizumab 840 mg administered every 2 weeks and 1,200 mg administered every 3 weeks are comparable. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks after multiple doses. The maximum systemic accumulation ratio across dosing regimens is 3.3.

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, 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). The effect of moderate or severe hepatic impairment (bilirubin > 1.5 × to 3 × ULN and any AST or 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 fetus resulting in fetal death. Administration of atezolizumab could cause fetal harm, including embryo-fetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for no more than 24 hours at 2 °C to 8 °C or 24 hours at ≤ 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 and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C).

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 a plastic, mist grey flip-off cap 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.

Do not shake.

Instructions for dilution

Important note: Do not administer the full content of the vial (1200 mg).

Fourteen 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 3.2 mg of atezolizumab **(840 mg/264 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.

No incompatibilities have been observed between atezolizumab and intravenous bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE) or polyolefin (PO). 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.

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
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Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

00031/0006

9. DATE OF SCIENTIFIC OPINION

11 March 2019

Additional information

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.atezolizumabeams@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 oncologist will also be provided with a physician pack containing all the relevant documents, including adverse events reporting form, needed to manage patients receiving atezolizumab under EAMS.

Medicines & Healthcare products Regulatory Agency

MHRA

Contact information

Contact details for reporting Adverse Events, Pregnancies or Breastfeeding, Overdose, Medication Error or Occupational Exposure:

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.atezolizumabeams@roche.com

Contact Details for Medical Information

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