PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Tecentriq® 840 mg (Concentrate for solution for infusion)

Tecentriq® 1 200 mg (Concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: atezolizumab

Tecentriq is supplied as single-use vials containing preservative-free, colourless to slightly yellow solution, at an active ingredient concentration of 60 mg/mL, as follows:

- 14 mL vial containing a total of 840 mg atezolizumab
- 20 mL vial containing a total of 1 200 mg atezolizumab

Contains sugar (sucrose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear, colourless to slightly yellowish liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metastatic urothelial carcinoma

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):

- after platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5 % (see section 5.1)

Early-stage non-small cell lung cancer (early-stage NSCLC)

Tecentriq as monotherapy is indicated as adjuvant treatment following resection and platinum-based chemotherapy for patients with stage II to IIIA (7th edition of the Union International Centre le Cancer/American Joint Committee on Cancer (UICC/AJCC)-staging system) NSCLC whose tumours have PD-L1 expression on ≥ 1 % tumour cells (TC).

Non-small cell lung cancer (NSCLC)

Tecentriq, combined with bevacizumab, paclitaxel and carboplatin is indicated as first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC). Patients with EGFR or ALK genomic tumour aberrations should have received targeted therapy, if clinically indicated, before receiving Tecentriq.

Tecentriq, combined with nab-paclitaxel and carboplatin as first-line treatment of patients with metastatic non-squamous non-small cell lung cancer who do not have EGFR or ALK genomic tumour aberrations.

Tecentriq as monotherapy is indicated for the first-line treatment of patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50 % tumour cells (TC) or ≥ 10 % tumour-infiltrating immune cells (IC) and who do not have EGFR or ALK genomic tumour aberrations.

Tecentriq as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with NSCLC who are ineligible for platinum- based chemotherapy and who do not have EGFR or ALK genomic tumor aberrations, who have:

- locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or
- metastatic NSCLC

Small cell lung cancer

Tecentriq, combined with carboplatin and etoposide for first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Triple-negative breast cancer (TNBC)

Metastatic breast cancer (mBC)

Tecentriq, combined with nab-paclitaxel is indicated for the treatment of patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1 ≥ 1 %, and who have not been given chemotherapy for metastatic disease.

Early breast cancer (eBC)

Tecentriq in combination with nab-paclitaxel and anthracycline-based chemotherapy, is indicated for the neoadjuvant treatment of patients with locally advanced or early TNBC.

Hepatocellular carcinoma (HCC)

Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

4.2 Posology and method of administration

General

Tecentriq must be administered as an intravenous infusion under the supervision of a qualified healthcare professional. Do not administer as an IV push or bolus. Full resuscitative facilities must be present.

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

Substitution by any other biological medicinal product requires the consent of the prescribing doctor.

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

Tecentriq monotherapy

If specified in the indication, adult patients should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (*see section 4.1 Therapeutic Indications*).

Tecentriq combination therapy

For the use of Tecentriq in combination therapy, please also refer to the full professional information for the combination product. Tecentriq should be administered prior to IV combination therapy if given the same day.

Table 1 Recommended dose for Tecentriq monotherapy by intravenous (IV) infusion

<table>
<tr><th>Indication</th><th>Recommended dose and schedule</th><th>Duration of treatment</th></tr>
<tr><td rowspan="2">1L cisplatin-ineligible mUC</td><td rowspan="3">• 840 mg every 2 weeks or
• 1 200 mg every 3 weeks or
• 1 680 mg every 4 weeks</td><td>Until loss of clinical benefit or unmanageable toxicity</td></tr>
<tr><td>1L NSCLC</td><td>Until loss of clinical benefit or unacceptable toxicity</td></tr>
<tr><td>Early-stage NSCLC</td><td>For 1 year unless disease recurrence or unacceptable toxicity.</td></tr>
</table>

Table 2 Recommended dose for Tecentriq combination therapy by intravenous (IV) infusion

Indication	Recommended dose and schedule		Duration of treatment
	Tecentriq	**Combination medicines**	
1L non-squamous metastatic NSCLC: Tecentriq with bevacizumab, paclitaxel, and carboplatin	*Induction Phase*: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	*Induction phase*: • Bevacizumab, paclitaxel, and then carboplatin are administered every 3 weeks. *Maintenance phase* • Bevacizumab is administered every 3 weeks.	
1L non-squamous metastatic NSCLC: Tecentriq with nab-paclitaxel and carboplatin	Tecentriq should be administered first when given on the same day. *Maintenance phase (without chemotherapy):* Tecentriq is administered according to its dosing schedules by IV infusion.	*Induction Phase*: • Nab-paclitaxel and carboplatin are administered every 3 weeks. • For each 21-day cycle, nab-paclitaxel and carboplatin are administered on day 1. • In addition, nab-paclitaxel is administered on days 8 and 15.	*Induction phase*: • Four or six cycles *Maintenance phase*: • Until disease progression or unmanageable toxicity.

Indication	**Recommended dose and schedule**		**Duration of treatment**
	Tecentriq	**Combination medicines**	
1L ES-SCLC: Tecentriq with carboplatin and etoposide		*Induction Phase*: • Carboplatin and etoposide are administered by IV infusion every three weeks. • Carboplatin and etoposide are administered on day 1 of each cycle, and etoposide is also administered on days 2 and 3.	
Locally advanced or early TNBC with chemotherapy	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered prior to chemotherapy when given on the same day.	The chemotherapy regimen consists of sequential nab-paclitaxel (125 mg/m^2 by IV infusion administered once every week for 12 doses), and an anthracycline + cyclophosphamide combination (by IV infusion administered once every 2 weeks for 4 doses).	Until disease progression or unmanageable toxicity. For neoadjuvant treatment of locally advanced or early TNBC, Tecentriq should be administered with chemotherapy, as part of a complete

Indication	Recommended dose and schedule		Duration of treatment
	Tecentriq	**Combination medicines**	
			treatment regimen
1L unresectable locally advanced or metastatic TNBC Tecentriq with nab-paclitaxel	•840 mg every 2 weeks or •1 200 mg every 3 weeks or •1 680 mg every 4 weeks	Tecentriq should be administered prior to nab-paclitaxel when given on the same day. 100 mg/m^2 nab-paclitaxel is administered on days 1, 8 and 15 of each 28-day cycle.	Until disease progression or unmanageable toxicity. Until disease progression or unmanageable toxicity
HCC: Tecentriq with bevacizumab	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	Tecentriq should be administered prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg body weight every 3 weeks.	Until loss of clinical benefit or unmanageable toxicity.

Delayed or Missed Doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

Dose Modifications

No dose reductions of Tecentriq are recommended.

Dose modifications for immune-mediated adverse reactions

Recommendations for specific adverse drug reactions (see section 4.4, General and section 4.8) are presented in Table 3.

Table 3: Recommended dose modifications for specific adverse drug reactions

Adverse Reaction	Severity	Treatment modification
Immune-mediated Pneumonitis	Grade 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis in patients without Unresectable Hepatocellular Carcinoma (HCC)	Grade 2 (ALT or AST > 3x ULN or blood bilirubin > 1,5x ULN for more than 5-7 days)	Withhold[1]
	Grade 3 or 4 (ALT or AST > 5,0x ULN or blood bilirubin > 3x ULN)	Permanently discontinue
Immune-mediated hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN If AST/ALT is > 1 to ≤ 3x ULN at baseline and increases to > 5x to ≤ 10x ULN If AST/ALT is > 3x to ≤ 5x ULN at baseline and increases to > 8x to ≤ 10x ULN	Withhold[1]
	If AST/ALT increases to > 10x ULN or total bilirubin increases to > 3x ULN	Permanently discontinue
Immune-mediated colitis	Grade 2 diarrhoea or colitis	Withhold[1]
	Grade 3 diarrhoea or colitis	Withhold[1] Initiate IV corticosteroids and convert to oral corticosteroids after improvement

Adverse Reaction	Severity	Treatment modification
	Grade 4 diarrhoea or colitis	Permanently discontinue
Immune-mediated hypothyroidism	Symptomatic	Withhold[2] Initiate thyroid hormone replacement therapy
Immune-mediated hyperthyroidism	Symptomatic	Withhold[2] Initiate anti-thyroid therapy as needed
Immune-mediated adrenal insufficiency	Symptomatic	Withhold[1]
Immune-mediated hypophysitis	Grade 2 or 3	Withhold[1]
	Grade 4	Permanently discontinue
Immune-mediated type 1 diabetes	For ≥ Grade 3 hyperglycemia (fasting glucose > 250 mg/dL)	Withhold[2] Initiate insulin
Immune-mediated Meningitis, encephalitis, myasthenic syndrome/ myasthenia gravis, Guillain-Barré syndrome	All grades	Permanently discontinue
Immune-mediated pancreatitis	Grade 2 or 3 ≥ Grade 3 increased serum amylase or lipase levels (> 2,0 ULN)	Withhold[1]
	Grade 4 or any grade recurrent pancreatitis	Permanently discontinue

Adverse Reaction	Severity	Treatment modification
Immune-mediated myocarditis	Grade 2 or above	Permanently discontinue
Immune-mediated myositis	Grade 2 or 3	Withhold
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue
Immune-mediated nephritis	Grade 2 (creatinine level > 1,5 – 3,0x baseline or > 1,5 – 3,0x ULN)	Withhold[1]
	Grade 3 (creatinine level > 3,0x baseline or > 3,0 – 6,0 x ULN) or 4 (creatinine level > 6,0 x ULN)	Permanently discontinue
Immune-mediated pericardial disorders	Grade 1 pericarditis	Withhold[3]
	Grade 2 or above	Permanently discontinue
Infusion related reactions	Grade 1 or 2	Reduce rate of infusion or withhold treatment Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	Withhold[1]
	Grade 4	Permanently discontinue[1]

Adverse Reaction	Severity	Treatment modification
	or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	

[1] Treatment with corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq may be resumed in patients with complete or partial resolution (Grade 0 to 1) within 12 weeks, and after corticosteroids have been reduced to ≤ 10 mg/day oral prednisone or equivalent.

[2] Treatment with Tecentriq may be resumed when symptoms are controlled and the patient is clinically stable.

[3] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately

[4] Regardless of severity

For other immune-related reactions, based on the type and severity of the reaction, treatment with Tecentriq should be withheld for Grades 2 or 3 immune-mediated adverse reactions 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 Tecentriq 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 Tecentriq should be permanently discontinued for Grade 4 immune-related adverse reactions, or when unable to reduce corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Special Dosage Instructions

Paediatric use

Tecentriq is not approved for use in patients under the age of 18 years. The safety and efficacy of Tecentriq in this population has not been established. Tecentriq did not demonstrate clinical benefit in paediatric patients in a clinical trial (see section 5.2, Pharmacokinetics in Special Populations).

Geriatric use

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see section 5.2, Pharmacokinetics in Special Populations).

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see section 5.2, Pharmacokinetics in Special Populations).

Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. There are no data in patients with moderate or severe hepatic impairment (see section 5.2, Pharmacokinetics in Special Populations).

Instructions for dilution: see Special Instructions for use, Handling and Disposal, section 6.6.

Incompatibilities: see section 6.2

4.3 Contraindications

Tecentriq is contraindicated in patients with a known hypersensitivity to atezolizumab or any of the excipients.

Live vaccines should not be used while receiving Tecentriq. See section 4.4.

Pregnancy and lactation, see section 4.6.

4.4 Special warnings and precautions for use

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption should not take Tecentriq.

Tecentriq contains sucrose which may have an effect on the control of your blood sugar if you have diabetes mellitus.

Patients who had received or were to receive live vaccines were excluded from the clinical trials due to danger of systemic proliferation of the virus. The use of live virus vaccines is thus contraindicated with Tecentriq. The time that should pass before a live vaccine can

be used since the last dose should be 5,5 x the typical elimination half-life ($t_{1/2}$) of 27 days, i.e.: 148,5 days.

General

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Immune-mediated pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. See section 4.2 for recommended dose modifications.

Immune-mediated hepatitis

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with Tecentriq. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline. See section 4.2 for recommended dose modifications.

Immune-mediated colitis

Cases of diarrhoea or colitis have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of colitis. See section 4.2 for recommended dose modifications.

Immune-mediated endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Monitor thyroid function prior to and periodically during treatment with Tecentriq. Consider appropriate management of patients with abnormal thyroid function tests at baseline. Patients with abnormal thyroid function tests who are asymptomatic may receive Tecentriq. See section 4.2 for recommended dose modifications.

Immune-mediated meningoencephalitis

Meningoencephalitis has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. See section 4.2 for recommended dose modifications

Immune-mediated neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, were observed in patients receiving Tecentriq (see section 4.8). Patients should be monitored for symptoms of motor and sensory neuropathy. See section 4.2 for recommended dose modifications.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. See section 4.2 for recommended dose modifications.

Immune-mediated myocarditis

Myocarditis, including fatal cases, has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. See section 4.2 for recommended dose modifications.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis. See section 4.2 for recommended dose modifications.

Immune-mediated nephritis

Nephritis has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for changes in renal function. See section 4.2 for recommended dose modifications

Infusion related reactions

Infusion related reactions (IRRs) have been observed in clinical trials with Tecentriq (see section 4.8). See section 4.2 for recommended dose modifications.

Immune-mediated severe cutaneous adverse reactions

Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving Tecentriq. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, Tecentriq should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see section 4.2).

For suspected SCARs patients should be referred to a dermatologist for further diagnosis and management. Tecentriq should be withheld with patients with suspected SJS or TEN. For confirmed SJS or TEN, Tecentriq should be permanently discontinued.

Caution should be used when considering the use of Tecentriq in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer medicines.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for clinical signs and symptoms of pericardial disorders. Refer to section 4.2 for recommended dose modifications.

Special populations

Patients with autoimmune disease were excluded from clinical trials with Tecentriq. In the absence of data, Tecentriq is not recommended for use in patients who have autoimmune diseases.

Embryo-foetal toxicity

Based on the mechanism of action, the use of Tecentriq may cause foetal harm. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death.

Pregnant women should be advised of the potential risk to the foetus. Women of childbearing potential should be advised to use highly effective contraception during treatment with Tecentriq and for 5 months after the last dose (see section 4.6, Females and Males of Reproductive Potential).

4.5 Interaction with other medicines and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Females and Males of Reproductive Potential

Fertility

Based on animal studies, Tecentriq may impair fertility in females of reproductive potential while receiving treatment.

Contraception

Female patients of childbearing potential should use highly effective contraception and take active measures to avoid pregnancy while undergoing Tecentriq treatment and for at least 5 months after the last dose (see section 4.4, General, and Embryo-foetal Toxicity).

Pregnancy

Tecentriq is contraindicated for use during pregnancy (see section 4.4, Embryo-foetal Toxicity). Based on the mechanism of action, the use of Tecentriq may cause foetal harm. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased immune-related rejection of the developing foetus resulting in foetal death.

Lactation

Women receiving Tecentriq must not breast feed their infants, or for 5 months after the last dose. Monoclonal antibodies, such as Tecentriq, are secreted in milk and may harm the infant. (See section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. Infusion reactions may impair a patient's ability to drive or to handle machines.

4.8 Undesirable effects

a. Summary of the safety profile:

Clinical Trials

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Tecentriq monotherapy

The safety of Tecentriq monotherapy is based on pooled data in 3 178 patients with multiple tumour types, with supporting data from the estimated cumulative exposure in > 13 000 patients across all clinical trials. Table 4 summarises the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq.

b. Tabulated list of adverse reactions

Table 4 Summary of adverse reactions occurring in patients treated with Tecentriq monotherapy in clinical trials

ADR (MedDRA)	Tecentriq (n=3 178)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Thrombocytopenia [n]	116 (3,7 %)	27 (0,8 %)	0 (0 %)	Common
Cardiac Disorders				
Myocarditis [a]	-	-	-	Rare
Pericardial disorders [ee,ff]	45 (1,4 %)	22 (0,7 %)	2 (<0,1 %)	Common
Endocrine Disorders				
Hypothyroidism [b]	164 (5,2 %)	6 (0,2 %)	0 (0 %)	Common
Hyperthyroidism [c]	30 (0,9 %)	1 (< 0,1 %)	0 (0 %)	Uncommon
Adrenal insufficiency [d]	11 (0,3 %)	2 (< 0,1 %)	0 (0 %)	Uncommon
Hypophysitis	2 (<0,1%)	0 (0 %)	0 (0 %)	Rare
Diabetes mellitus [e]	10 (0,3 %)	6 (0,2 %)	0 (0 %)	Uncommon
Gastrointestinal Disorders				
Diarrhoea [o]	626 (19,7 %)	36 (1,1 %)	0 (0 %)	Very Common
Dysphagia	82 (2,6 %)	16 (0,5 %)	0 (0 %)	Common
Colitis [f]	34 (1,1 %)	18 (0,6 %)	0 (0 %)	Common
Nausea	747 (23,5 %)	35 (1,1 %)	0 (0 %)	Very Common
Vomiting	477 (15,0 %)	26 (0,8 %)	0 (0 %)	Very Common
Abdominal pain	268 (8,4 %)	34 (1,1 %)	0 (0 %)	Common
Pancreatitis [g]	18 (0,6 %)	13 (0,4 %)	0 (0 %)	Uncommon
Oropharyngeal pain [q]	131 (4,1 %)	0 (0 %)	0 (0 %)	Common
General Disorders and Administration				
Chills	207 (6,5 %)	2 (< 0,1 %)	0 (0 %)	Common
Fatigue	1 142 (35,9 %)	109 (3,4 %)	0 (0%)	Very Common
Asthenia	461 (14,5 %)	63 (2,0 %)	0 (0 %)	Very Common
Influenza like illness	186 (5,9 %)	1 (< 0,1 %)	0 (0 %)	Common
Pyrexia	638 (20,1 %)	17 (0,5 %)	0 (0 %)	Very Common
Infusion related reaction [h]	34 (1,1 %)	5 (0,2 %)	0 (0 %)	Common
Hepatobiliary Disorders				
Increased ALT	167 (5,3%)	46 (1,4 %)	0 (0 %)	Common
Increased AST	180 (5,7 %)	46 (1,4 %)	0 (0 %)	Common
Hepatitis [i]	62 (2,0 %)	25 (0,8 %)	1 (< 0,1 %)	Common
Immune System Disorders				

ADR (MedDRA)	**Tecentriq (n=3 178)**			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Hypersensitivity	36 (1,1 %)	3 (< 0,1 %)	0 (0 %)	Common
Infections and infestations				
Urinary tract infection [p]	368 (11,6 %)	86 (2,7 %)	0 (0 %)	Very Common
Metabolism and Nutrition Disorders				
Decreased appetite	810 (25,5 %)	35 (1,1 %)	0 (0 %)	Very Common
Hypokalaemia [v]	142 (4,5 %)	33 (1,0 %)	0 (0%)	Common
Hyponatraemia [w]	171 (5,4 %)	98 (3,1 %)	0 (0 %)	Common
Hyperglycaemia	103 (3,2 %)	32 (1,0 %)	0 (0 %)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	441 (13,9 %)	23 (0,7 %)	0 (0 %)	Very Common
Back pain	487 (15,3 %)	52 (1,6 %)	0 (0 %)	Very Common
Musculoskeletal pain [r]	489 (15,4 %)	36 (1,1 %)	0 (0 %)	Very Common
Myositis [t,u]	13 (0,4 %)	5 (0,2 %)	0 (0 %)	Uncommon
Nervous System Disorders				
Headache	352 (11,1 %)	10 (0,3 %)	0 (0 %)	Very common
Guillain-Barré syndrome [j]	5 (0,2 %)	4 (0,1 %)	0 (0 %)	Uncommon
Meningoencephalitis [k]	14 (0,4 %)	6 (0,2 %)	0 (0 %)	Uncommon
Myasthenic syndrome	1 (< 0,1 %)	0 (0 %)	0 (0 %)	Rare
Renal and urinary disorders				
Increased blood creatinine [aa]	171 (5,4 %)	14,0 (0,4 %)	0 (0 %)	Common
Nephritis [s]	3 (< 0,1 %)	1 (< 0,1 %)	0 (0 %)	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	660 (20,8 %)	9 (0,3 %)	0 (0 %)	Very Common
Dyspnoea	651 (20,5 %)	117 (3,7 %)	1 (< 0,1 %)	Very Common
Hypoxia	75 (2,4 %)	36 (1,1 %)	0 (0 %)	Common
Pneumonitis [l]	87 (2,7 %)	27 (0,8 %)	1 (< 0,1 %)	Common
Nasopharyngitis [bb]	280 (8,8 %)	0 (0 %)	0 (0 %)	Common
Skin and Subcutaneous Tissue Disorders				
Rash [m]	619 (19,5 %)	34 (1,1 %)	1 (< 0,1 %)	Very Common
Pruritus	400 (12,6 %)	7 (0,2 %)	0 (0 %)	Very Common
Dry skin	187 (5,9 %)	1 (< 0,1 %)	0 (0 %)	Common

ADR (MedDRA)	**Tecentriq (n=3 178)**			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Psoriatic conditions [cc]	19 (0,6 %)	2 (< 0,1 %)	0 (0 %)	Uncommon
Severe cutaneous adverse reactions [dd]	22 (0,7 %)	3 (< 0,1 %)	1 (< 0,1 %)	Uncommon
Vascular Disorders				
Hypotension	102 (3,2 %)	20 (0,6 %)	0 (0 %)	Common

a. Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

b. Includes reports of hypothyroidism, increased blood thyroid stimulating hormone, decreased blood thyroid stimulating hormone, thyroiditis, autoimmune hypothyroidism, euthyroid sick syndrome, myxoedema, abnormal thyroid function test, acute thyroiditis, decreased thyroxine

c. Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos

d. Includes reports of adrenal insufficiency, primary adrenal insufficiency

e. Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis

f. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, ulcerative colitis

g. Includes reports of pancreatitis, autoimmune pancreatitis, acute pancreatitis, increased lipase and increased amylase

h. includes infusion related reaction and cytokine release syndrome

i. Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, acute hepatitis, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, esophageal varices haemorrhage, esophageal varices

j. Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy

k. Includes reports of encephalitis, meningitis, photophobia

l. Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.

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

n. Includes reports of thrombocytopenia and decreased platelet count

o. Includes reports of diarrhoea, frequent bowel movements, and gastrointestinal hypermotility

p. Includes reports of urinary tract infection, cystitis, pyelonephritis, Escherichia urinary tract infection, acute pyelonephritis, bacterial urinary tract infection, kidney infection, fungal urinary tract infection, pseudomonal urinary tract infection

q. Includes reports of oropharyngeal pain, throat irritation, oropharyngeal discomfort

r. Includes reports of musculoskeletal pain, myalgia, bone pain

s. Includes reports of nephritis and Henoch-Schonlein Purpura nephritis

t. Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, present myoglobin urine

u. Fatal cases have been reported in studies outside the pooled dataset

v. Includes reports of hypokalaemia and decreased blood potassium

w. Includes reports of hyponatraemia and blood sodium decreased

x. Includes reports of hypoxia, oxygen saturation decreased, PO_2 decreased

y. Includes reports of hypophysitis and temperature regulation disorder

z. Includes report of myasthenia gravis

aa. Includes reports of blood creatinine increased and hypercreatininaemia

bb. Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea

cc. Includes reports of dermatitis psoriasiform and psoriasis.

dd. Includes reports of bullous dermatitis, exfoliative rash, erythema multiforme, generalised exfoliative dermatitis, toxic skin eruption, toxic epidermal necrolysis

ee. Includes reports of pericarditis, pericardial effusion, cardiac tamponade and constrictive pericarditis

ff. Reported from post marketing experience outside the pooled dataset. The frequency is based on the program-wide exposure.

Tecentriq combination therapy

Additional ADRs identified in clinical trials (not reported in monotherapy trials) associated with the use of Tecentriq in combination therapy across multiple indications are summarised in Table 5. ADRs with a clinically relevant difference when compared to monotherapy (refer to Table 4) are also presented.

Table 5: Summary of adverse reactions occurring in patients treated with Tecentriq combination therapy in clinical trials

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4 371)			
System Organ Class	**All Grades (%)**	**Grade 3-4 (%)**	**Grade 5 (%)**	**Frequency (All Grades)**
Blood and Lymphatic System Disorders				
Anaemia[*]	1 608 (36,8 %)	631 (14,4 %)	0 (0 %)	Very Common
Lymphopenia[*, k]	145 (3,3 %)	63 (1,4 %)	0 (0 %)	Common
Neutropenia[*,+,a]	1 565 (35,8 %)	1 070 (24,5 %)	6 (0, 1 %)	Very Common
Thrombocytopenia[*,‡, b]	1 211 (27,7 %)	479 (11,0 %)	1 (< 0, 1 %)	Very Common
Leukopenia[*,l]	571 (13,1 %)	245 (5,6 %)	0 (0 %)	Very common
Endocrine Disorders				
Hypothyroidism[*,‡,c]	586 (13,4 %)	9 (0,2 %)	0 (0 %)	Very Common
Hyperthyroidism[‡]	193 (4,4 %)	7 (0,2 %)	0 (0 %)	Common
Adrenal insufficiency[+,‡, d]	40 (0,9 %)	8 (0,2 %)	1 (< 0,1 %)	Uncommon
Hypophysitis[‡,e]	13 (0,3 %)	5 (0,1 %)	0 (0 %)	Uncommon
Gastrointestinal Disorders				
Constipation[*]	1 123 (25,7 %)	24 (0,5 %)	0 (0 %)	Very Common
Stomatitis[*]	351 (8,0 %)	23 (0,5 %)	0 (0 %)	Common
General Disorders and Administration Site Conditions				
Peripheral oedema[*]	451 (10,3 %)	11 (0,3 %	0 (0 %)	Very Common
Infections & Infestations				
Lung infection[+,*, h]	564 (12,9 %)	226 (5,2 %)	26 (0,6 %)	Very Common
Investigations				
Increased blood alkaline phosphatase	200 (4,6 %)	26 (0,6 %)	0 (0 %)	Common
Metabolism and Nutrition Disorders				
Hypomagnesaemia[*]	403 (9,2 %)	22 (0,5 %)	0 (0 %)	Common
Nervous System Disorders				
Dizziness[*]	408 (9,3 %)	9 (0,2 %)	0 (0 %)	Common
Dysgeusia[*]	269 (6,2 %)	0 (0,0 %)	0 (0 %)	Common

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4 371)			
System Organ Class	**All Grades (%)**	**Grade 3-4 (%)**	**Grade 5 (%)**	**Frequency (All Grades)**
Peripheral neuropathy*,f	1 007 (23,0 %)	107 (2,4 %)	0 (0 %)	Very Common
Syncope*	68 (1,6 %)	36 (0,8 %)	0 (0 %)	Common
Renal and Urinary Disorders				
Nephritis ‡,l	23 (0,5 %)	15 (0,3 %)	0 (0 %)	Uncommon
Proteinuria*,g	359 (8,2 %)	61 (1,4 %)	0 (0 %)	Common
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia*	236 (5,4 %)	4 (0,1 %)	0 (0 %)	Common
Nasopharyngitis o	442 (10,1 %)	1 (< 0,1 %)	0 (0 %)	Very common
Skin and Subcutaneous Tissue disorders				
Alopecia n	1 152 (26,4 %)	3 (< 0,1 %	0 (0 %)	Very common
Severe cutaneous adverse reactions p	27 (0,6 %)	8 (0,2 %)	0 (0 %)	Uncommon
Vascular Disorders				
Hypertension*,m	611 (14,0 %)	258 (5,9 %)	0 (0 %)	Very common

∗ ADR occurring at a frequency ≥ 5 % (All grades) or ≥ 2 % (Grades 3-4) compared to the control arm.

+ Fatal cases of neutropenia, adrenal insufficiency and lung infection have been observed when Tecentriq is given in combination treatment

‡ Observed rate in the combination represents a clinically relevant difference in comparison to Tecentriq monotherapy

a. Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia

b. Includes reports of thrombocytopenia and decreased platelet count

c. Includes reports of hypothyroidism, increased blood thyroid stimulating hormone, decreased blood thyroid stimulating hormone, autoimmune thyroiditis, goitre, thyroiditis, decreased free thyroxine, decreased free tri−iodothyronine, thyroid disorder, increased free thyroxine, increased thyroxine, decreased tri−iodothyronine, increased free

tri−iodothyronine, abnormal blood thyroid stimulating hormone, euthyroid sick syndrome, myxedema coma, abnormal thyroid function test, decreased thyroxine, abnormal tri−iodothyronine

d. Includes reports of adrenal insufficiency, acute adrenocortical insufficiency, secondary adrenocortical insufficiency, adrenocorticotropic abnormal hormone stimulation test, addison's disease, adrenalitis, adrenocorticotropic hormone deficiency

e. Includes reports of hypophysitis and temperature regulation disorder

f. Includes reports of peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, autoimmune neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy and toxic neuropathy, peripheral nerve infection

g. Includes reports of proteinuria, protein urine present, haemoglobinuria, and nephrotic syndrome

h. Includes reports of pneumonia, bronchitis, lower respiratory tract infection, infective exacerbation of chronic obstructive airway disease, infectious pleural effusion, atypical pneumonia, lung abscess, pleural infection, pyopneumothorax

i. Includes reports of decreased white blood cell count and leukopenia

j. Includes reports of hypomagnesaemia and decreased blood magnesium

k. Includes reports of lymphopenia and decreased lymphocyte count

l. Includes reports of nephritis, tubulointerstitial nephritis, autoimmune nephritis, allergic nephritis, glomerulonephritis, nephrotic syndrome and mesangioproliferative glomerulonephritis

m. Includes reports of hypertension, increased blood pressure, hypertensive crisis, increased blood pressure systolic, diastolic hypertension, blood pressure inadequately controlled and hypertensive retinopathy

n. Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis and hypotrichosis

o. Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea

p. Includes reports of bullous dermatitis, exfoliative rash, erythema multiforme, generalised dermatitis exfoliative, toxic skin eruption, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, cutaneous vasculitis

c. Additional information for selected adverse reactions

The data below reflect information for significant adverse reactions for Tecentriq monotherapy. Details for the significant adverse reactions for Tecentriq when given in combination are presented if clinically relevant differences were noted in comparison to Tecentriq monotherapy. See section 4.4, General, for management of the following:

Immune-mediated pneumonitis

Pneumonitis occurred in 2,7 % (87/3 178) of patients who received Tecentriq monotherapy. Of the 87 patients, one event was fatal. The median time to onset was 3,4 months (range: 0,1 to 24,8 months). The median duration was 1,4 months (range 0 to 21,2+ months; + denotes a censored value). Pneumonitis led to discontinuation of Tecentriq in 12 (0,4 %) patients. Pneumonitis requiring the use of corticosteroids occurred in 1,6 % (51/3 178) of patients receiving Tecentriq.

Immune-mediated hepatitis

Hepatitis occurred in 2,0 % (62/3 178) of patients who received Tecentriq monotherapy. Of the 62 patients, two events were fatal. The median time to onset was 1,5 months (range 0,2 to 18,8 months). The median duration was 2,1 months (range 0 to 22,0+ months; + denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 6 (0,2 %) patients. Hepatitis requiring the use of corticosteroids occurred in 0,6 % (18/3 178) of patients receiving Tecentriq.

Immune-mediated colitis

Colitis occurred in 1,1 % (34/3 178) of patients who received Tecentriq. The median time to onset was 4,7 months (range 0,5 to 17,2 months). The median duration was 1,2 months (range: 0,1 to 17,8+ months; + denotes a censored value). Colitis led to discontinuation of Tecentriq in 8 (0,3 %) patients. Colitis requiring the use of corticosteroids occurred in 0,6 % (19/3 178) of patients receiving Tecentriq.

Immune-mediated endocrinopathies

Thyroid Disorders

Hypothyroidism occurred in 5,2 % (164/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 4,9 months (range 0 to 31,3 months).

Hyperthyroidism occurred in 0,9 % (30/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 2,1 months (range 0,7 to 15,7 months). The median duration was 2,6 months (range: 0+ to 17,1+ months; + denotes a censored value).

Hyperthyroidism occurred in 4,9 % (23/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Hyperthyroidism led to discontinuation in 1 (0,2 %) patient.

Adrenal Insufficiency

Adrenal insufficiency occurred in 0,4 % (12/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 5,5 months (range: 0,1 to 19,0 months). The median duration was 16,8 months (range: 0 to 16,8 months). Adrenal insufficiency led to discontinuation of Tecentriq in 1 (< 0,1 %) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0,3 % (9/3 178) of patients receiving Tecentriq.

Adrenal insufficiency occurred in 1,5 % (7/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Adrenal insufficiency requiring the use of corticosteroids occurred in 0,8 % (4/473) of patients receiving Tecentriq in combination with carboplatin and nab-paclitaxel.

Hypophysitis

Hypophysitis occurred in < 0,1 % (2/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 7,2 months (range: 0,8 to 13,7 months). One patient required the use of corticosteroids and treatment with Tecentriq was discontinued.

Hypophysitis occurred in 0,8 % (3/393) of patients who received Tecentriq with bevacizumab, paclitaxel, and carboplatin. The median time to onset was 7,7 months (range: 5,0 to 8,8 months). Two patients required the use of corticosteroids. Hypophysitis led to the discontinuation of treatment in one patient.

Diabetes Mellitus

Diabetes mellitus occurred in 0,3 % (11/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 4,2 months (range 0,1 to 9,9 months). The median duration was 1,6 months (range: 0,1 to 15,2+ months; + denotes a censored value). Diabetes mellitus led to the discontinuation of Tecentriq in 3 (< 0,1 %) patients.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0,4 % (13/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 0,5 months (range 0 to 12,5 months). The median duration was 0,7 months (range 0,2 to 14,5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0,2 % (6/3 178) of patients receiving Tecentriq and led to discontinuation of Tecentriq in 4 (0,1 %) patients.

Immune-mediated neuropathies

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0,2 % (5/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 7,0 months (range: 0,6 to 8,1 months). The median duration was 8,0 months (0,6 to 8,3+ months; + denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq in 1 (< 0,1 %) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0,1 % (2/3 178) of patients receiving Tecentriq.

Immune-mediated pancreatitis

Pancreatitis, including increased amylase and increased lipase, occurred in 0,6 % (18/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 5,0 months (range: 0,3 to 16,9 months). The median duration was 0,8 months (range 0,1 to 12,0+ months; + denotes a censored value). Pancreatitis led to discontinuation of Tecentriq in 3 (< 0,1 %) patients. Pancreatitis requiring the use of corticosteroids occurred in 0,1 % (4/3 178) of patients receiving Tecentriq.

Immune-mediated myositis

Myositis occurred in 0,4 % (13/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 5,1 months (range: 0,7 to 11,0 months). The median duration was 5,0 months (range 0,7 to 22,6+ months, + denotes a censored value). Myositis led to discontinuation of Tecentriq in 1 (< 0,1 %) patient. Myositis requiring the use of corticosteroids occurred in 0,2 % (7/3 178) of patients receiving Tecentriq.

Immune-mediated nephritis

Nephritis, occurred in < 0,1 % (3/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 13,1 months (range: 9,0 to 17,5 months). The median duration was 2,8 days (range 0,5 to 9,5+ months; + denotes a censored value). Nephritis led to discontinuation of Tecentriq in 2 (< 0,1 %) patients. One patient required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0,7 % (22/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 5,9 months (range 0,1 to 15,5 months). The median duration was 1,6 months (range 0 to 22,1+ months; + denotes a censored value). SCARs led to discontinuation of Tecentriq in 3 (< 0,1 %) patients. SCARs requiring the use of systemic corticosteroids occurred in 0,2 % (6/3 178) of patients receiving Tecentriq monotherapy.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1,4 % (45/3 178) of patients who received Tecentriq monotherapy. The median time to onset was 1,4 months (range 0,2 to 17,5 months). The median duration was 1,4 months (range 0 to 19,3 months). Pericardial disorders led to discontinuation of Tecentriq in 3 (<0,1 %) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0,2 % (7/3178) patients.

Post Marketing Experience

Cases of pericardial disorders have been reported during post-marketing use of Tecentriq (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no information on overdose with Tecentriq.

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 agent, humanised immunoglobulin G1 (IgG1) monoclonal antibody. ATC Code – L01FF05

Mechanism of action

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

Atezolizumab is an Fc-engineered humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1 / PD-1 pathway-mediated inhibition of the immune response, including reactivating the antitumor immune response. Atezolizumab leaves the PD-L2/PD-1 interaction intact. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

5.2 Pharmacokinetic properties

The pharmacokinetics of atezolizumab have been characterised in patients in multiple clinical trials at doses 0,01 mg/kg to 20 mg/kg every 3 weeks including the fixed dose of 1 200 mg. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 - 20 mg/kg with a linear two-compartment disposition model with first-order elimination. 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.

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

Absorption

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

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution (V1) is 3,28 L and volume at steady-state (Vss) is 6,91 L in the typical patient.

Metabolism

The metabolism of Tecentriq 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 ($t_{1/2}$) is 27 days.

Pharmacokinetics in Special Populations

Paediatric population

The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (<18 years, n=69) and young adult patients (18-30 years, n=18), show that the clearance and volume of distribution of atezolizumab were comparable between paediatric patients receiving 15 mg/kg and young adult patients receiving 1 200 mg of atezolizumab every 3 weeks when normalised by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children <2 years is limited thus no definitive conclusions can be made.

Geriatric population

No dedicated studies of Tecentriq have been conducted in geriatric 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; Special Dosage Instructions).

Renal impairment

No dedicated studies of Tecentriq have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1,73 m^2; n=208) or moderate (eGFR 30 to 59 mL/min/1,73 m^2. n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1,73 m^2; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1,73 m^2; n=8) (see section 4.2; Special Dosage Instructions).

Hepatic impairment

No dedicated studies of Tecentriq 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 (bilirubin > 3,0· ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 4.2; Special Dosage Instructions).

Immunogenicity

There is the potential for immune response to atezolizumab. Across multiple phase III studies, 13,1 % to 36,4 % of patients developed treatment-emergent anti-drug antibodies (ADAs) and 4,3 % to 19,7 % of patients developed neutralising antibodies (NAbs). ADA and NAb status appeared to have no clinically relevant impact on pharmacokinetics. Although some variability was observed across the studies, overall, ADA positivity appeared to have no clinically relevant impact on efficacy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Glacial acetic acid,

L-histadine,

polysorbate 20,

sucrose,

water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store between 2 - 8 °C. Do not freeze. Do not shake.

Keep the vial in the outer carton, in order to protect from light, until required for use.

Keep out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

The diluted solution for infusion should be used immediately. If the solution is not used immediately, it can be stored for up to 30 days at 2 °C – 8 °C, or 8 hours at ambient temperature (≤ 25 °C), if prepared under aseptic conditions.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

6.5 Nature and contents of container

Type I glass-vial with a butyl rubber stopper containing 20 mL of solution.

Pack of one vial.

6.6 Special Instructions for Use, Handling and Disposal

Instructions for dilution

Tecentriq should be prepared by a healthcare professional using aseptic technique. Use a sterile needle to prepare Tecentriq. Withdraw the required volume of Tecentriq liquid concentrate from the vial and dilute to the required administration volume with 0,9 % sodium chloride solution. Dilute with 0,9 % Sodium Chloride Injection only. After dilution, the final concentration of the diluted solution should be between 3,2 and 16,8 mg/mL.

This medicine must not be mixed with other medicines.

No preservative is used in Tecentriq therefore each vial is for single use only. Discard any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBERS

Tecentriq® 840 mg 54/30.1/0060

Tecentriq® 1 200 mg 54/30.1/0061

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 29 September 2020

10. DATE OF REVISION OF THE TEXT: 13 February 2025

Tecentriq® 1 200 mg/20 mL:	Namibia: NS2 22/30.1/0025	Botswana: S2 BOT2103779
Tecentriq® 840 mg/14 mL:	Namibia: NS2 22/30.1/0024	Botswana: S2 BOT2103778

Approved Manufacturers:

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