Tecentriq®▼ (atezolizumab): Important Safety Information to Minimise the Risks of Immune-Related Adverse Reactions

FOR HEALTHCARE PROFESSIONALS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See box on page 27 for details on how to report.

This is additional risk minimisation material and is provided by Roche Products (Ireland) Limited as a condition of the Tecentriq® marketing authorisation.

This material should be read in conjunction with the Summary of Product Characteristics (SmPC) which is available on www.medicines.ie and www.ema.europa.eu

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MT V 11.1.0

Indications

For the approved indications of Tecentriq®, please refer to the current Summary of Product Characteristics which is available on www.medicines.ie or www.ema.europa.eu.

Important Safety Information

This guide is intended to provide information about the management of certain important identified risks when prescribing Tecentriq®, including immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, meningoencephalitis, nephritis, pancreatitis, myocarditis, myositis and infusion-related reactions.

All patients receiving treatment with Tecentriq® must be given a Patient Alert Card by their healthcare professional to educate them about the symptoms of immune-related adverse reactions and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to any healthcare professional who may treat them.

To obtain copies of the Patient Alert Card, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland by mail, telephone [00 353 (0)1 4690700] or email [Ireland.drug_surveillance_centre@roche.com].

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Explore the Following Sections to Learn More About Managing Immune-Related Adverse Reactions:

What is Tecentriq®?

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 reactivation of the antitumour immune response.

Common Adverse Reactions

The safety of atezolizumab as monotherapy is based on pooled data in 3,178 patients across multiple tumour types. The most common adverse reactions (>10%) were fatigue (35.9%), decreased appetite (25.5%), nausea (23.5%), cough (20.8%), dyspnoea (20.5%), rash (19.5%), diarrhoea (19.7%), back pain (15.3%), pyrexia (20.1%), asthenia (14.5%), vomiting (15.1%), arthralgia (13.9%), musculoskeletal pain (13.1%), pruritus (12.6%), and urinary tract infection (11.6%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The safety of atezolizumab given in combination with other agents, has been evaluated in 1,345 patients across multiple tumour types. The most common adverse reactions (≥20%) were fatigue (33.2%), rash (30.4%), nausea (30.2%), peripheral neuropathy (28.3%), diarrhoea (27.6%), arthralgia (24.7%), constipation (24.0%), decreased appetite (23.3%), anaemia (23.0%) and musculoskeletal pain (22.9%).

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin
In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

Recognise and Manage Immune-Related Adverse Reactions Associated With Therapy

Tecentriq® is associated with immune-related adverse reactions.

- Early identification and timely intervention can help to reduce the severity and duration of immune-related adverse reactions.
- Other aetiologies for adverse events should be considered.

For suspected immune-related adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reactions:

- Withhold Tecentriq® and administer corticosteroids. Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over at least 1 month.
  - Rapid tapering may lead to worsening of adverse reaction.
- Consider to restart Tecentriq® within 12 weeks after adverse reaction onset date if the adverse reaction improves to and remains at Grade ≤1 and corticosteroid dose is ≤10 mg prednisone or equivalent per day.
- Permanently discontinue Tecentriq® if any Grade ≥3 toxicity occurs a second time and for any Grade 4 immune-related adverse reaction, except for endocrinopathies that are controlled with replacement hormones.
- Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

If immunosuppression with corticosteroids is used to treat an immune-related adverse reaction, a taper of at least 1 month duration should be initiated upon improvement to ≤Grade 1.

- Rapid tapering may lead to worsening of adverse reaction.

Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Tecentriq® should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids[1] or other immunosuppressants.

Tecentriq® should also be permanently discontinued for immune-related adverse reactions that persist despite treatment modifications (described in this guide) or if a reduction of corticosteroid dose to ≤10 mg prednisone or equivalent per day cannot be achieved within 12 weeks of adverse reaction onset date. Please see the next section for detailed information regarding individual immune-related adverse reactions and management recommendations.

[1] *Immunosuppressive doses of corticosteroids are defined by prednisone >10 mg daily PO, or equivalent.*

Immune-Related Pneumonitis

- Cases of pneumonitis, including fatal cases, have been observed with Tecentriq® treatment.
- Monitor patients for signs and symptoms of pneumonitis (see below).

Pneumonitis

Signs and symptoms

- Breathing difficulties or cough
- Radiographic changes (e.g. focal ground glass opacities, patchy infiltrates)
- Dyspnoea
- Hypoxia

Rule out infectious and disease-related aetiologies.

Pneumonitis occurred in 2.7% (87/3,178) of patients who received atezolizumab monotherapy. Of the 87 patients, one experienced a fatal event. The median time to onset was 3.4 months (range 3 days to 24.8 months). The median duration was 1.4 months (range 0 day to 21.2+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (51/3,178) of patients receiving atezolizumab monotherapy.

Managing Immune-Related Pneumonitis

NCI CTCAE v4	**Pneumonitis Grade 2** (Symptomatic; medical intervention indicated; worsens from baseline)	**Pneumonitis Grade 3-4** (Severe symptoms; O_2 indicated. G4: life threatening; urgent intervention indicated)
Tecentriq® treatment and monitoring	**Withhold Tecentriq®; monitor daily; consider bronchoscopy and lung biopsy and refer to a respiratory physician**	**Permanently discontinue Tecentriq®; monitor daily, consider bronchoscopy and lung biopsy and refer to a respiratory physician**
Corticosteroids	Prednisone 1-2 mg/kg or equivalent per day	Prednisone 1-2 mg/kg or equivalent per day
Follow-up	Reassess signs and symptoms every 1-2 weeks	Reassess signs and symptoms every 3-5 days
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month; treatment with Tecentriq® may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3/4	**If no improvement after 48 hr.:** Consider adding additional immunosuppressive medication

Immune-Related Hepatitis

- Cases of hepatitis, including fatal cases, have been observed with Tecentriq® treatment.
- Monitor patients for signs and symptoms of hepatitis (see below).
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with Tecentriq® and as indicated based on clinical evaluation.

Hepatitis

Signs and symptoms

- Elevations in transaminases
- Total bilirubin elevations
- Jaundice
- Right sided abdominal pain
- Tiredness

Rule out infectious and disease-related aetiologies.

Hepatitis occurred in 2.0% (62/3,178) of patients who received atezolizumab monotherapy. Of the 62 patients, two experienced a fatal event. The median time to onset was 1.5 months (range 6 days to 18.8 months). The median duration was 2.1 months (range 2 days to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 6 (<0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.6% (18/3,178) of patients receiving atezolizumab monotherapy.

Managing Immune-Related Hepatitis

NCI CTCAE v4	**Hepatitis Grade 2** (AST/ALT >3.0–5.0 × ULN or bilirubin >1.5–3.0 × ULN)	**Hepatitis Grade 3–4** (G3: AST/ALT >5.0–20.0 × ULN or bilirubin >3.0–10.0 × ULN; G4: AST/ALT >20.0 × ULN or bilirubin >10.0 × ULN)
Tecentriq® treatment and monitoring	**Withhold Tecentriq® if persists >5–7 days; repeat LFTs every 1–3 days; ultrasound or CT scan; and refer to a gastroenterologist**	**Permanently discontinue Tecentriq®; daily LFTs; consider liver biopsy; and refer to a gastroenterologist**
Corticosteroids	Prednisone 1–2 mg/kg or equivalent per day, if Tecentriq® withheld	Prednisone 1–2 mg/kg or equivalent per day
Follow-up	Reassess LFTs every 1–2 weeks	Reassess LFTs every 3–5 days
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month; Tecentriq® may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3/4	**If no improvement after 48 hr.:** Consider adding additional immunosuppressive medication

ALT: alanine aminotransaminase; AST: aspartate aminotransaminase; CT: computed tomography; LFTs: liver function tests; ULN: upper limit of normal.

Immune-Related Colitis

- Colitis has been observed with Tecentriq® treatment.
- Monitor patients for diarrhoea and additional symptoms of colitis (see below).

Colitis

Signs and symptoms

- Watery, loose or soft stools; increase in bowel movements or stool frequency
- Abdominal pain
- Mucus or blood in stool

Rule out infectious and disease-related aetiologies.

Colitis occurred in 1.1% (34/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 4.7 months (range 15 days to 17.2 months). The median duration was 1.2 months (range 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 8 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (19/3,178) of patients receiving atezolizumab monotherapy.

Managing Immune-Related Colitis

NCI CTCAE v4	**Diarrhoea / Colitis Grade 2** (Increase of 4–6 stools / day or moderate increase in ostomy output compared to baseline); or abdominal pain, mucus or blood in the stool	**Diarrhoea / Colitis Grade 3** (Increase of ≥7 stools / day or severe increase in ostomy output compared to baseline, incontinence, limiting self care ADL, hospitalisation indicated); or severe abdominal pain; peritoneal signs	**Diarrhoea / Colitis Grade 4** (Life-threatening consequences; urgent intervention indicated)
Tecentriq® treatment/other therapy and monitoring	**Withhold Tecentriq®; symptomatic therapy; monitor every 2-3 days**	**Withhold Tecentriq®; symptomatic therapy; monitor daily**	**Permanently discontinue Tecentriq®; symptomatic therapy; monitor daily; consider endoscopy with biopsy**
Corticosteroids	Prednisone 1–2 mg/kg or equivalent per day, if symptoms persists >5 days or recur	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement
Follow-up	Reassess weekly	Reassess every 3-5 days	Reassess every 1-3 days
	If improves to ≤Grade 1: Taper steroids over at least 1 month; atezolizumab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper steroids over at least 1 month; Tecentriq® may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3 or 4	**If no improvement, worsens or recurs:** Treat as Grade 4	**If no improvement:** Consider adding additional immunosuppressive medication and refer to a gastroenterologist for additional care

ADL: activities of daily living.

Immune-Related Endocrinopathies

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus including diabetic ketoacidosis, and hypophysitis have been observed with Tecentriq® treatment.
- Monitor patients for signs and symptoms of endocrinopathies (see below) and for changes in thyroid function and glucose control (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Appropriate management of patients with abnormal thyroid function tests at baseline should be considered. Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab.
- Blood and urine glucose and ketones should be tested, and fasting glucose sampled to confirm hyperglycaemia.
- Monitor patients for signs and symptoms of immune-related diabetes mellitus, including diabetic ketoacidosis.
- Pituitary hormone levels and function tests and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Endocrinopathies

Signs and symptoms

- Fatigue
- Headache
- Mental status change
- Heat or cold intolerance
- Tachycardia or bradycardia
- Unusual bowel habits
- Weight change
- Polyuria / polydipsia
- Blurred vision

Unless an alternate aetiology has been identified, signs and symptoms of endocrinopathies should be conservatively considered immune-related.

Thyroid disorders

Hypothyroidism occurred in 5.2% (164/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 4.9 months (range 0 days to 31.3 months). Hyperthyroidism occurred in 0.9% (30/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 2.1 months (range 21 days to 15.7 months).

Adrenal insufficiency

Adrenal insufficiency occurred in 0.4% (12/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range 3 days to 19 months). The median duration was 16.8 months (range: 0 day to 16.8 months). Adrenal insufficiency led to discontinuation of atezolizumab in 1 (<0.1%) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (9/3,178) of patients receiving atezolizumab monotherapy.

Diabetes mellitus

Diabetes mellitus occurred in 0.3% (11/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 3.6 months (range 3 days to 9.9 months). Diabetes mellitus led to the discontinuation of atezolizumab in 0.1% (3/3,178) patients.

Hypophysitis

Hypophysitis occurred in <0.1% (2/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 7.2 months (range: 24 days to 13.7 months). One patient required the use of corticosteroids and treatment with atezolizumab was discontinued.

Hypophysitis occurred in 0.8% (3/393) of patients who received atezolizumab 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.

Managing Immune-Related Endocrinopathies

	Symptomatic Hypothyroidism	Symptomatic Hyperthyroidism	Symptomatic Adrenal insufficiency (Patients with unexplained symptoms should be investigated for the presence of pituitary or adrenal endocrinopathies)	Hyperglycemia (Grade 3–4) or DKA (G3: Fasting glucose value >250–500 mg/dL or >13.9–27.8 mmol/L; hospitalisation indicated; G4: Fasting glucose value >500 mg/dL or >27.8 mmol/L with life-threatening consequences)
Tecentriq® treatment/other therapy and monitoring	**Withhold Tecentriq®; initiate thyroid replacement therapy as needed; TSH and clinical evaluation every 3–5 days**	**Withhold Tecentriq®; initiate symptomatic therapy including antithyroid medicinal product as needed; TSH, free T3/T4 every 3–5 days**	**Withhold Tecentriq®; initiate physiological corticosteroid and mineral corticosteroid replacement or hormone replacement therapy as needed;** TSH, prolactin and morning cortisol may help differentiate primary adrenal insufficiency from primary pituitary process; consider appropriate imaging	**Withhold Tecentriq®; confirm fasting glucose, C-peptide and anti-insulin antibodies; arterial blood gas for metabolic status; consider endocrinologist referral;** Start insulin replacement and management per local guidelines
Corticosteroids	–	–	Treat with an initial dose of IV methylprednisolone 1–2 mg/kg per day followed by oral prednisone 1–2 mg/kg per day, when symptoms improve	–
Follow-up	Reassess weekly	Reassess weekly	Reassess every 1-3 days	Once hyperglycemia or DKA has resolved, reassess every cycle with random blood glucose and per local diabetes management guidelines
	If improves: Restart Tecentriq® when symptoms are controlled by thyroid replacement and TSH levels are decreasing	**If improves:** Restart Tecentriq® when symptoms are controlled by **antithyroid medicinal product**	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month; Treatment may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and patient is stable on replacement therapy (if required)	**If improves and glucose levels are stable on insulin replacement:** Restart Tecentriq®
	If no improvement or worsens: **Permanently discontinue Tecentriq® and refer to an endocrinologist for additional care**	**If no improvement or worsens:** **Permanently discontinue Tecentriq® and refer to an endocrinologist for additional care**	**If worsens or symptomatic adrenal insufficiency recurs:** **Permanently discontinue Tecentriq® and refer to an endocrinologist for additional care**	**If no improvement or worsens despite appropriate diabetes management:** **Permanently discontinue Tecentriq® and refer to an endocrinologist for additional care**

DKA: diabetic ketoacidosis; TSH: thyroid stimulating hormone, T3: triiodothyronine; T4: thyroxine.

Managing Immune-Related Endocrinopathies

	Hypophysitis (pan-hypopituitarism) Grade 2–3 (G2: Moderate; minimal intervention indicated; or limiting age appropriate instrumental ADL; G3: Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting self care ADLs)	**Hypophysitis (pan-hypopituitarism) Grade 4** (G4: Life-threatening consequences or urgent intervention indicated)
Tecentriq® treatment/ other therapy and monitoring	**Withhold Tecentriq®; refer to endocrinologist; monitor pituitary hormone levels and pituitary function; initiate hormone replacement therapy as needed; pituitary imaging by MRI**	**Permanently discontinue Tecentriq®; refer to endocrinologist; monitor pituitary hormone levels and pituitary function; initiate hormone replacement therapy; pituitary imaging by MRI**
Corticosteroids	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement
Follow-up	Reassess every 1-3 days	Reassess daily
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month; Treatment may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and patient is stable on replacement therapy (if required)	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If worsens or recurs: Treat as Grade 4	**If no improvement or worsens:** Consider adding additional immunosuppressive medication and refer to an endocrinologist for additional care

ADL: activities of daily living.

Immune-Related Meningoencephalitis

- Meningoencephalitis has been observed with Tecentriq® treatment.
- Monitor patients for signs and symptoms of meningitis or encephalitis (see below).

Meningoencephalitis

Signs and symptoms

- Headache
- Mental status change, confusion, altered or depressed level of consciousness
- Photophobia
- Seizure
- Motor or sensory dysfunction
- Meningeal irritability, nuchal rigidity

Rule out infectious and disease-related aetiologies.

Meningoencephalitis occurred in 0.4% (13/3,178) of patients who received atezolizumab monotherapy. The median time to onset ranged from 15 days (range: 0 day to 12.5 months). The median duration was 26 days (range from 6 days to 14.5+ months; + denotes a censored value). Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3,178) of patients receiving atezolizumab and all four patients discontinued atezolizumab.

Managing Immune-Related Meningoencephalitis

Tecentriq® treatment and monitoring	**Permanently discontinue Tecentriq®;** urgent CT or MRI of the brain, lumbar puncture, daily clinical evaluation (rule out metabolic or electrolyte imbalance, infectious aetiologies, progression of malignancy or paraneoplastic syndromes)
Corticosteroids	Treat with IV corticosteroids (methylprednisolone 1–2 mg/kg or equivalent per day) followed by oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) after improvement
Follow-up	Reassess every 1-3 days
	If improves to ≤Grade 1: Taper steroids over at least 1 month
	If not improving after 48 hr. or worsening: Consider adding additional immunosuppressive medication and refer to a neurologist for additional care

CT: computed tomography; MRI: magnetic resonance imaging.

Immune-Related Neuropathies

- Myasthenic syndrome/myasthenia gravis and Guillain-Barré syndrome have been observed with Tecentriq® treatment.
- Monitor patients for signs and symptoms of immune-mediated neuropathies (see below).

Motor and Sensory Nerve Disorders

Signs and symptoms

- Muscle weakness (including ocular muscles)
- Fatigability
- Difficulty swallowing
- Paraesthesia or altered sensation
- Ascending or progressive paralysis
- Respiratory muscle weakness
- Meningeal irritability, nuchal rigidity

Rule out infectious and disease-related aetiologies.

Immune-related neuropathies
Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 8.0 months (range 18 days to 8.3+ months; + denotes a censored value). Guillain-Barré syndrome led to the discontinuation of atezolizumab in 1 patient (<0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/3,178) of patients receiving atezolizumab monotherapy.

Myasthenic syndrome
Myasthenia gravis occurred in <0.1% (1/3,178) of patients who received atezolizumab monotherapy. The time to onset was 1.2 months

Managing Immune-Related Neuropathies

	Myasthenia gravis, Myasthenic syndrome, Guillain-Barré syndrome (Patients should be investigated for a thymoma and presence of paraneoplastic syndromes that may present with motor and sensory nerve disorders)
Tecentriq® treatment/ other therapy and monitoring	**Permanently discontinue Tecentriq®; treat as per institutional guidelines**; neurological assessment, pulmonary function testing, autoantibodies, lumbar puncture, edrophonium test, nerve stimulation, electromyography, as appropriate. Consider referral to a neurologist
Corticosteroids	**As per institutional guidelines for Myasthenia Gravis and Guillain-Barré syndrome.** Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg/day of prednisone or equivalent) should be considered
Follow-up	Reassess daily
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month (if corticosteroids started)
	If no improvement after 28 hr.: Consider adding additional immunosuppressive medication and refer to a neurologist for additional care

Immune-Related Pancreatitis

- Cases of immune-related pancreatitis and increases in serum amylase and lipase levels, have been observed with Tecentriq® treatment.
- Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Pancreatitis, including amylase increased and lipase increased, occurred in 0.6% (18/3,178) of patients who received atezolizumab monotherapy. The median time to onset was 5.0 months (range: 9 days to 16.9 months). The median duration was 24 days (range 3 days to 12.0+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 3 (<0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (4/3,178) of patients receiving atezolizumab monotherapy.

Managing Immune-Related Pancreatitis

NCI CTCAE v4	**Amylase or Lipase elevation Grade 3–4** (G3: amylase/lipase >2.0–5.0 × ULN; G4: amylase/lipase >5.0 × ULN)	**Pancreatitis Grade 2 or 3** (G2: enzyme elevation or radiologic findings only; G3: severe pain; vomiting)	**Pancreatitis Grade 4** (Life-threatening consequences; urgent intervention indicated)
Tecentriq® treatment/other therapy	**Withhold Tecentriq®;** Monitor amylase/lipase daily	**Withhold Tecentriq®;** Monitor amylase/lipase and clinical condition daily **Medical management of pancreatitis**	**Permanently discontinue Tecentriq®;** Monitor amylase/lipase and clinical condition daily **Aggressive medical management of pancreatitis**
Corticosteroids	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)
Follow-up	Reassess every 1-3 days	Reassess every 1-3 days	Reassess daily
	If improves to ≤Grade 1: Treatment with Tecentriq® may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤10 mg oral prednisone or equivalent per day	**If improves to ≤Grade 1:** Treatment with Tecentriq® may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤10 mg oral prednisone or equivalent per day	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If recurs: Treat as Grade 3 or 4 elevation, unless signs/ symptoms of pancreatitis	**If recurs: Permanently discontinue Tecentriq® and refer to a gastroenterologist for additional care**	**If worsens: Consider additional immunosuppressive medications and refer to a gastroenterologist for additional care**

ULN: upper limit of normal.

Immune-Related Myocarditis

- Cases of immune-related myocarditis have been observed with Tecentriq® treatment.
- Patients should be closely monitored for signs and symptoms that are suggestive of acute myocarditis.

Immune-Related Myocarditis

Signs and symptoms

- Shortness of breath
- Decreased exercise tolerance
- Fatigability
- Chest pain
- Swelling of ankles or legs
- Irregular heart beat
- Fainting

Rule out infectious and disease-related aetiologies.

Myocarditis occurred in <0.1% (2/8,000) of patients across all atezolizumab clinical trials in multiple tumour types and treatment combinations. The time to onset was 18 and 33 days. Both patients required corticosteroids and discontinued atezolizumab.

Managing Immune-Related Myocarditis

NCI CTCAE v4	**Myocarditis Grade 1** (Asymptomatic with laboratory [e.g. BNP] or cardiac imaging abnormalities)	**Myocarditis Grade 2** (Symptoms with mild to moderate activity or exertion)	**Myocarditis Grade 3–4** (G3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; G4: Life-threatening consequences; urgent intervention indicated [e.g. continuous IV therapy or mechanical haemodynamic support])
Tecentriq® treatment/other therapy and monitoring	Refer patient to cardiologist; initiate treatment as per institutional guidelines	**Withhold Tecentriq®;** refer patient to cardiologist, monitor clinical condition daily **Medical management of myocarditis**	**Permanently discontinue Tecentriq®;** refer patient to cardiologist, monitor clinical condition daily **Aggressive medical management of myocarditis**
Corticosteroids	–	Methylprednisolone 1-2 mg/kg IV daily or equivalent and convert to 1-2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1-2 mg/kg IV daily or equivalent and convert to 1-2 mg/kg oral prednisone or equivalent per day (once symptoms improve)
Follow-up	–	Reassess every 1-3 days	Reassess daily
		If improves to ≤Grade 1: Treatment with Tecentriq® may be resumed when myocarditis improves to Grade 0 or Grade 1 within 12 weeks, or symptoms of myocarditis have resolved, and corticosteroids have been reduced to ≤10 mg oral prednisone or equivalent per day	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
		If recurs: Permanently discontinue Tecentriq® and refer to a cardiologist for additional care	**If worsens: Consider additional immunosuppressive medications and refer to a cardiologist for additional care**

BNP: B-Natriuretic Peptide.

Immune-Related Nephritis

- Nephritis has been observed with Tecentriq® treatment.
- The most common presentation is asymptomatic increase in serum creatinine level in the absence of alternative etiologies (e.g. prerenal and postrenal causes, and concomitant medications).
- Monitor patients for signs and symptoms below.
- Patients should be monitored for changes in renal function.

Nephritis

Signs and symptoms

- Increase in serum creatinine
- Decrease in the amount of urine
- Changes in the appearance of urine, including blood in urine
- Fluid retention (e.g. swelling in the extremities or face)
- Hypertension
- Loss of appetite

Rule out infectious and disease-related aetiologies.

Nephritis occurred in <0.1% (3/3,178) of patients who received atezolizumab. The median time to onset was 13.1 months (range: 9.0 to 17.5 months). The median duration was 2.8 months (range 15 days to 9.5+ months; + denotes a censored value). Nephritis led to discontinuation of atezolizumab in 2 (<0.1%) patients. One patient required corticosteroids and discontinued atezolizumab.

Managing Immune-Related Nephritis

NCI CTCAE v5	**Nephritis Grade 2** (Serum creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	**Nephritis Grade 3–4** G3: (Serum creatinine >3.0 x baseline; >3.0 - 6.0 x ULN) G4: (Serum creatinine >6.0 x ULN)
Tecentriq® treatment and monitoring	**Withhold Tecentriq®; monitor kidney function, including creatinine, closely until resolution; refer patient to renal specialist**	**Permanently discontinue Tecentriq®; monitor kidney function, including creatinine, daily until resolution; refer patient to renal specialist and consider renal biopsy**
Corticosteroids	Prednisone 1-2 mg/kg or equivalent per day	Prednisone 1-2 mg/kg or equivalent per day
Follow-up	Reassess signs and symptoms every 2-3 days	Reassess signs and symptoms daily
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month; treatment with Tecentriq® may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3/4	**If no improvement after 48 hr.:** Consider adding additional immunosuppressive medication

ULN: upper limit of normal.

Immune-Related Myositis

- Myositis has been observed with Tecentriq® treatment.
- Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury.
- Symptoms may include muscle weakness and/or pain, skin rash (in dermatomyositis), urine with dark brown or reddish colour, nausea and vomiting.
- Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase) and imaging (electromyography/MRI) features and is confirmed with a muscle biopsy.
- Monitor patients for signs and symptoms described above.

Rule out infectious and disease-related aetiologies.

Myositis occurred in 0.4% (12/3,178) of patients who received Tecentriq® monotherapy. The median time to onset was 5.4 months (range: 0.7 to 11.0 months). The median duration was 3.5 months (range 0.1 to 22.6+ months; + denotes a censored value). Myositis led to discontinuation of Tecentriq® in 1 (<0.1%) patient. Seven (0.2%) patients required the use of corticosteroids.

Managing Immune-Related Myositis

NCI CTCAE v5	**Myositis Grade 2-3** G2: Moderate pain associated with weakness; pain limiting instrumental activities of daily living (ADL) G3: Pain associated with severe weakness; limiting self care ADL	**Myositis Grade 4 or 3 recurrent** G3: Pain associated with severe weakness; limiting self care ADL G4: Life-threatening consequences; urgent intervention required
Tecentriq® treatment and monitoring	Withhold Tecentriq®; monitor serum creatinine kinase closely until resolution; refer patient to a rheumatologist or neurologist. **Medical management of myositis**	Permanently discontinue Tecentriq® for Grade 4 or Grade 3 recurrent myositis; monitor serum creatinine kinase, daily until resolution; refer patient to a rheumatologist or neurologist. Respiratory support may be required for severe cases. **Aggressive medical management of myositis**
Corticosteroids	Prednisone 1-2 mg/kg or equivalent per day	If severely compromised (e.g. cardiac or respiratory symptoms, that severely limit mobility), initiate corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus. Upon improvement, convert to prednisone 1-2 mg/kg or equivalent per day
Follow-up	Reassess signs and symptoms every 2-3 days	Reassess signs and symptoms daily
	If improves to ≤Grade 1: Taper corticosteroids over at least 1 month; treatment with Tecentriq® may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 4 or Grade 3 recurrent	**If no improvement after 48 hr.:** Consider adding additional immunosuppressive medication

Infusion-Related Reactions (IRR)

NCI CTCAE v4	**IRR Grade 2** (Infusion interruption indicated but responds promptly to symptomatic treatment)	**IRR Grade 3–4** G3: (Prolonged; recurrence of symptoms following initial improvement; hospitalisation indicated) G4: (Life-threatening consequences; urgent intervention indicated)
Tecentriq® treatment/ other therapy	**Reduce infusion rate or interrupt Tecentriq® infusion; aggressive symptomatic treatment**	**Stop infusion of Tecentriq®; Aggressive medical management which may include oral or IV antihistamine, antipyretic, epinephrine, glucocorticoids, bronchodilators and oxygen**
Monitoring (acute event)	Per local Infusion Centre IRR protocol	Per local Infusion Centre IRR protocol; Evaluation in Emergency Department or Hospital
Corticosteroids	–	As per local medical management of IRR
Follow-up	Reassess per local Infusion Centre protocols and at the end of infusion	Evaluate in Emergency Department or Hospital
	If improves to ≤Grade 1: The infusion rate at restart should be half of the infusion rate that was in progress at the time of onset of the event; at the next cycle, consider administration of oral premedication with antihistamine and antipyretic	**Permanently discontinue Tecentriq®**
	If no improvement, worsens or recurs: Treat as Grade 3/4	–

Reporting of suspected adverse events or reactions

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions (see details below). Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:
Post: The Drug Surveillance Centre, Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland.
Telephone: 00 353 (0)1 4690700
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at: http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:
Post: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta
Email: postlicensing.medicinesauthority@gov.mt

Further Information

For additional copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material.
Alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland by mail, telephone [00 353 (0)1 4690700], or email [ireland.drug_surveillance_centre@roche.com].

For further information about this medicine, please contact Medical Information at Roche Products (Ireland) Limited by telephone [00 353 (0)1 4690700] or email [Ireland.druginfo@roche.com].

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