יולי 2022

Tecentriq® 60mg/ml
atezolizumab
Concentrate for solution for infusion

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים שבוצעו בעלון לרופא של התכשיר טיסנטריק המתייחסים לניהול תופעות לוואי.

בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויות הרשומות לתכשיר בישראל:

Urothelial Carcinoma

- TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours have a PD-L1 expression ≥ 5%.
- TECENTRIQ is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

Non-Small Cell Lung Cancer

- TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an approved test, with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated only after failure of appropriate targeted therapies.
- TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ is indicated for the treatment of patients with metastatic NSCLC who are naïve to anti-PD-L1 or anti-PD-1 therapies and have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.

Locally Advanced or Metastatic Triple-Negative Breast Cancer

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

Small Cell Lung Cancer

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma

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

Melanoma

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

למידע נוסף יש לעיין בעלון לרופא כפי שנשלח למשרד הבריאות.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס ע"י פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079
טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,

לילי אדר
רוקחת ממונה

בתאור צפרי-חגג
מחלקת רישום

עדכונים מהותיים בעלון לרופא

בסעיף DOSAGE AND ADMINISTRATION עודכן המידע הבא:

2.8 Dosage Modifications for Adverse Reactions

No dose reductions of TECENTRIQ are is recommended. Recommendations for dosage modifications are provided in Table 1.

In general, withhold TECENTRIQ for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TECENTRIQ for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for TECENTRIQ for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a] of Adverse Reaction[1]	Dosage Modifications
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold[b] dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver in patients with cancers other than HCC[2] *[see Warnings and Precautions (5.1)]*	AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or total Total bilirubin increases to more than 1.5 and up to 3 times the upper limit of normal (ULN)	Withhold[b] dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT increases to more than 8 times the upper limit of normal (ULN) or total Total bilirubin increases to more than 3 times the upper limit of normal (ULN)	Permanently discontinue

Adverse Reaction	Severity[a] ~~of Adverse Reaction[1]~~	Dosage Modifications~~[2]~~
Hepatitis with tumor involvement of the liver[c] ~~in patients with HCC[2] *[see Warnings and Precautions (5.1)]*~~	~~• AST or ALT is within normal limits at baseline and increases to more than 3 and up to 10 times the ULN~~ Baseline AST or ALT is more than 1 and up to 3 times ULN ~~at baseline~~ and increases to more than 5 and up to 10 times ~~the~~ ULN ~~1. or~~ • Baseline AST or ALT is more than 3 and up to 5 times ULN ~~at baseline~~ and increases to more than 8 and up to 10 times ~~the~~ ULN	Withhold[b] ~~dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)~~
	AST or ALT increases to more than 10 times ~~the~~ ULN or total Total bilirubin increases to more than 3 times ~~the~~ ULN	Permanently discontinue
~~Colitis or diarrhea *[see Warnings and Precautions (5.1)]*~~	~~Grade 2 or 3~~	~~Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)~~
	~~Grade 4~~	~~Permanently discontinue~~
Endocrinopathies ~~(including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus) *[see Warnings and Precautions (5.1)]*~~	Grades ~~2,~~ 3, or 4	Withhold ~~dose~~ until ~~Grade 1 or resolved and~~ clinically stable ~~on hormone replacement therapy~~ or permanently discontinue depending on severity.
Nephritis with Renal Dysfunction	Grades 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue

Adverse Reaction	Severity[a] ~~of Adverse Reaction[1]~~	Dosage Modifications~~s~~
~~Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (5.1)]*~~	~~Grade 3~~	~~Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)~~
	~~Grade 4~~	~~Permanently discontinue~~
~~Infections *[see Warnings and Precautions (5.2)]*~~	~~Grade 3 or 4~~	~~Withhold dose until Grade 1 or resolved~~
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.~~3~~2)]*	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue
~~Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)~~	~~Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last TECENTRIQ dose~~	~~Permanently discontinue~~
~~Inability to taper corticosteroid~~	~~Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last TECENTRIQ dose~~	~~Permanently discontinue~~
~~Recurrent Grade 3 or 4 adverse reaction~~	~~Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction~~	~~Permanently discontinue~~

[1]~~[a]~~ Based on ~~National Cancer Institute~~ Common Terminology Criteria for Adverse Events (~~NCI~~ CTCAE), version 4.~~0~~

[2] ~~HCC: Hepatocellular Carcinoma~~

[b.] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

[c.] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TECENTRIQ based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson syndrome, TEN = toxic epidermal necrolysis

בסעיף Warnings and Precautions עודכן המידע הבא:

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

[…]

In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis ~~or interstitial lung disease, defined as requiring use of systemic corticosteroids, including fatal cases~~. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

~~Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher pneumonitis. Withhold or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.8)].*~~

[…]

Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis ~~or diarrhea, defined as requiring use of systemic corticosteroids~~. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

~~Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 or 3 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 diarrhea or colitis. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*~~

[…]

Immune-Mediated Hepatitis

~~TECENTRIQ can cause liver test abnormalities and immune-mediated hepatitis, defined as requiring use of systemic corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher elevations of ALT, AST and/or total bilirubin. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.8)].*~~

TECENTRIQ can cause immune-mediated hepatitis.

[…]

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

~~T~~ECENTRIQ can cause primary or secondary adrenal insufficiency. ~~Monitor patients for clinical signs and symptoms of adrenal insufficiency.~~ For Grade 2 or higher adrenal insufficiency, initiate ~~prednisone 1to 2 mg/kg/day or equivalents, followed by a taper and~~ symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue~~Interrupt~~ TECENTRIQ ~~based~~ depending on ~~the~~ severity *[see Dosage and Administration (2.8)]*.

[…]

Hypophysitis

~~T~~ECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. ~~For Grade 2 or higher hypophysitis, initiate prednisone 1□2 mg/kg/day or equivalents, followed by a taper and~~ Initiate hormone replacement ~~therapy~~ as clinically indicated. Withhold or permanently discontinue~~Interrupt~~ TECENTRIQ ~~based~~ depending on ~~the~~ severity *[see Dosage and Administration (2.8)]*.

[…]

Thyroid ~~Disorders~~disorders:

TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management ~~of~~ for hyperthyroidism as clinically indicated. Withhold or permanently discontinue~~Continue~~ TECENTRIQ ~~for hypothyroidism and interrupt for hyperthyroidism based~~ depending on ~~the~~ severity *[see Dosage and Administration (2.8)]*.

[…]

Type 1 Diabetes Mellitus , which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue~~Interrupt~~ TECENTRIQ ~~based~~ depending on ~~the~~ severity *[see Dosage and Administration (2.8)]*.

[…]

בסעיף ADVERSE REACTIONS עודכן המידע הבא:

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors *[see Warnings and Precautions (5.3)]*