מרץ 2019

Tecentriq® 1200mg/20ml
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.

בהודעה זו מצוינים (בצבע צהוב) רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויות הרשומות לתכשיר בישראל:

Locally Advanced or Metastatic 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.

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.

Metastatic Non-Small Cell Lung Cancer

TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (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 these aberrations prior to receiving TECENTRIQ.

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,

בתאור צפרי-חגג
מחלקת רישום

לילי אדר
רוקחת ממונה

עדכונים מהותיים בעלון לרופא

בסעיף 2 Dosage and Administration עודכן המידע הבא:

2.2 Dosage Modifications for Adverse Reactions

No dose reductions of TECENTRIQ are recommended.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 3 or 4	Permanently discontinue
Hepatitis *[see Warnings and Precautions (5.2)]*	AST or ALT more than 3 and up to 8 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold 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 more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Colitis or diarrhea *[see Warnings and Precautions (5.3)]*	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 (5.4)]*	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (5.5)]*	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 (5.6)]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

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בסעיף 5 Warnings and Precautions עודכן המידע הבא:

5.1 Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids, including fatal cases.

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5.2 Immune-Mediated Hepatitis

TECENTRIQ can cause liver test abnormalities and immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

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5.5 Other Immune-Mediated Adverse Reactions

TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with TECENTRIQ, immune-mediated adverse reactions can also manifest after discontinuation of TECENTRIQ.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper. Interrupt or permanently discontinue TECENTRIQ, based on the severity of the reaction *[see Dosage and Administration (2.3)]*.

If uveitis occurs in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% in 2616 patients who received TECENTRIQ or were reported in other products in this class *[see Adverse Reactions (6.1)]*:

Cardiac: myocarditis

Dermatologic: bullous dermatitis, pemphigoid, erythema multiforme, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).

Gastrointestinal: pancreatitis, including increases in serum amylase or lipase levels

General: systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis

Hematological: autoimmune hemolytic anemia, immune thrombocytopenic purpura.

Musculoskeletal: myositis, rhabdomyolysis.

Neurological: Guillain-Barre syndrome, myasthenia syndrome/myasthenia gravis, demyelination, immune-related meningoencephalitis, aseptic meningitis, encephalitis, facial and abducens nerve paresis, polymyalgia rheumatica, autoimmune neuropathy, and Vogt-Koyanagi-Harada syndrome.

Ophthalmological: uveitis, iritis.

Renal: nephrotic syndrome, nephritis.

Vascular: vasculitis

5.6 Infections

TECENTRIQ can cause severe infections including fatal cases.
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5.7 Infusion-Related Reactions

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For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

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5.8 Embryo-Fetal Toxicity

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Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ.
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בסעיף 6 Adverse Reactions עודכן המידע הבא:

NSCLC

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The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (43.5%), decreased appetite (23.5%), dyspnea (22%), and cough (26.4%). The most common Grade 3–4 adverse reactions (≥ 2%) were dyspnea, pneumonia, fatigue, anemia, and pulmonary embolism.

Table 6: Adverse Reactions Occurring in ≥ 10% of Patients with NSCLC Receiving TECENTRIQ in OAK

	TECENTRIQ 1200 mg every 3 weeks n=609		Docetaxel 75 mg/m^2 every 3 weeks n=578	
Adverse Reaction[1]	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General				
Fatigue/Asthenia[2]	44	4	53	6
Pyrexia	18	<1	13	<1
Respiratory				
Cough[3]	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
Musculoskeletal				
Myalgia/pain[4]	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
Metabolism and Nutrition				
Decreased appetite	23	<1	24	1.6
Gastrointestinal				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
Skin				
Rash[5]	12	<1	10	0

[1] Graded per NCI CTCAE v4.0
[2] Includes fatigue and asthenia
[3] Includes cough and exertional cough
[4] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia
[5] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 7: Laboratory Abnormalities Worsening From Baseline Occurring in ≥ 20% of NSCLC Patients Receiving TECENTRIQ in OAK

Laboratory Abnormality	TECENTRIQ 1200 mg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
Grade	**All Grades[1] (%)[2]**	**Grade 3-4 (%)**	**All Grades[1] (%)[2]**	**Grade 3-4 (%)**
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21

[1] Graded according to NCI CTCAE version 4.0
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546–585) and docetaxel (range: 532–560)

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בסעיף 8 Use in Specific Populations עודכן המידע הבא:

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8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ *[see Use in Specific Populations (8.1)]*.