HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECENTRIQ safely and effectively. See full prescribing information for TECENTRIQ.

TECENTRIQ® (atezolizumab) injection, for intravenous use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage, Urothelial Carcinoma (1.1)	7/2018
Indications and Usage, Non-Small Cell Lung Cancer (1.2)	12/2018
Indications and Usage, Triple-Negative Breast Cancer (1.3)	3/2019
Dosage and Administration (2.1, 2.3, 2.4, 2.6)	3/2019
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7)	12/2018

INDICATIONS AND USAGE

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated in:

Urothelial Carcinoma

- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
  - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
  - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. (1.1)

  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.1)

Non-Small Cell Lung Cancer (NSCLC)

- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment, of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. (1.2)
- for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. (1.2)

Triple-Negative Breast Cancer (TNBC)

- in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.3)

DOSAGE AND ADMINISTRATION

Metastatic Urothelial Carcinoma or Previously Treated NSCLC

- TECENTRIQ 1200 mg intravenously (IV) over 60 minutes every 3 weeks.

First-line Treatment of Non-squamous NSCLC

- TECENTRIQ 1200 mg IV over 60 minutes, followed by bevacizumab, paclitaxel and carboplatin, on the same day, every 3 weeks for a maximum of 4-6 cycles. Following completion of chemotherapy, TECENTRIQ 1200 mg IV, following by bevacizumab, every 3 weeks.

Metastatic Treatment of TNBC

- TECENTRIQ 840 mg IV over 60 minutes, followed by 100 mg/m^2 paclitaxel protein-bound. For each 28day cycle, TECENTRIQ is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15.

If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Pneumonitis: Withhold or permanently discontinue based on severity of pneumonitis. (2.5, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold or permanently discontinue based on severity of transaminase or total bilirubin elevation. (2.5, 5.2)
- Immune-Mediated Colitis: Withhold or permanently discontinue based on severity of colitis. (2.5, 5.3)
- Immune-Mediated Endocrinopathies (2.5, 5.4):
  - Hypophysitis: Withhold based on severity of hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold based on severity of hyperthyroidism.
  - Adrenal Insufficiency: Withhold based on severity of adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold based on severity of hyperglycemia.
- Infections: Withhold for severe or life-threatening infection. (2.5, 5.6)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (2.5, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ as a single agent were fatigue, nausea, constipation, cough, dyspnea, and decreased appetite. (6.1)
- The most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ in combination with bevacizumab, paclitaxel, and carboplatin were fatigue/asthenia, alopecia, nausea, diarrhea, constipation, decreased appetite, arthralgia, hypertension, and peripheral neuropathy. (6.1)
- The most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ in combination with paclitaxel protein-bound were alopecia, peripheral neuropathies, fatigue, nausea, diarrhea, anemia, constipation, cough, headache, neutropenia, vomiting, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Urothelial Carcinoma

TECENTRIQ (atezolizumab) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
- are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s) *[see Clinical Studies (14.1)]*.

1.2 Metastatic Non-Small Cell Lung Cancer

- 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 (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.

1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ in combination with paclitaxel protein-bound is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer

Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ based on the PD-L1 expression on tumor-infiltrating immune cells *[see Clinical Studies (14.1)]*.

Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells *[see Clinical Studies (14.3)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer are available at: http://www.fda.gov/CcompanionDiagnostics

2.2 Recommended Dosage for TECENTRIQ for Locally Advanced or Metastatic Urothelial Carcinoma or Previously Treated NSCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

2.3 Recommended Dosage for TECENTRIQ for First-line Treatment of Metastatic Non-squamous NSCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes followed by bevacizumab, paclitaxel, and carboplatin, on Day 1 of each 21-day cycle for a maximum of 4 to 6 cycles of chemotherapy.

If the first infusion of TECENTRIQ is tolerated, all subsequent infusions may be delivered over 30 minutes.

After completion of chemotherapy, administer TECENTRIQ 1200 mg intravenously, followed by bevacizumab on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for bevacizumab, paclitaxel, and carboplatin for recommended dosing information.

2.4 Recommended Dosage for TECENTRIQ for Locally Advanced or Metastatic TNBC

The recommended dosage of TECENTRIQ is 840 mg administered as an intravenous infusion over 60 minutes, followed by 100 mg/m^2 paclitaxel protein-bound.

For each 28 day cycle, TECENTRIQ is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15 until disease progression or unacceptable toxicity.

TECENTRIQ and paclitaxel protein-bound may be discontinued for toxicity independently of each other. If the first infusion is tolerated, all subsequent infusions of TECENTRIQ may be delivered over 30 minutes. See also the prescribing information for paclitaxel protein-bound prior to initiation.

2.5 Dosage Modifications for Adverse Reactions

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

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity of Adverse Reaction[1]**	**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)

Adverse Reaction	Severity of Adverse Reaction[1]	Dosage Modifications
	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
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] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

2.6 Preparation and Administration

Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial.

Prepare the solution for infusion as follows:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of TECENTRIQ from the vial(s).
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution

This product does not contain a preservative.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze.

Do not shake.

Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Do not coadminister other drugs through the same intravenous line.

Do not administer as an intravenous push or bolus.

3 DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids, including fatal cases. 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 (2.5)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent *[see Adverse Reactions (6.1)]*, pneumonitis occurred in 2.5% of patients, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (< 0.1%) immune-mediated pneumonitis. The median time to onset of pneumonitis was 3.6 months (3 days to 20.5 months) and median duration of pneumonitis was 1.4 months (1 day to 15.1 months). Pneumonitis resolved in 67% of patients. Pneumonitis led to discontinuation of TECENTRIQ in 0.4% of the 2616 patients. Systemic corticosteroids were required in 1.5% of patients, including 0.8% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 45 days) followed by a corticosteroid taper.

The incidence of pneumonitis in 793 TECENTRIQ-treated patients in IMpower150 was 4.5%, including Grade 3-4 (1.8%) events. Systemic corticosteroids were required in 4% of patients, including 2.8% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 3 days (1 day to 43 days) followed by a corticosteroid taper.

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. 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 (2.5)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ *[see Adverse Reactions (6.1)]*, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (< 0.1%). The median time to onset of hepatitis was 1.4 months (1 day to 25.8 months) and median duration was 24 days (1 day to 13 months). Hepatitis resolved in 71% of patients. Hepatitis led to discontinuation of TECENTRIQ in 0.4% of 2616 patients. Systemic corticosteroids were required in 2% of the patients, with 1.3% requiring high-dose corticosteroids for a median duration of 3 days (1 day to 35 days) followed by a corticosteroid taper.

The incidence of hepatitis in 793 TECENTRIQ-treated patients in IMpower150 was 12.1%, including Grade 3-4 (4.0%) events. Systemic corticosteroids were required in 3.8% of the patients, with 2.6% requiring high-dose corticosteroids for a median duration of 7 days (1 day to 68 days) followed by a corticosteroid taper.

5.3 Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids. 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 (2.5) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent *[see Adverse Reactions (6.1)]*, diarrhea or colitis occurred in 20%, including Grade 3 (1.4%) events. The median time to onset of diarrhea or colitis was 1.5 months (1 day to 41 months). Diarrhea and colitis resolved in 85% of the patients. Diarrhea or colitis led to discontinuation of TECENTRIQ in 0.2% of 2616 patients. Systemic corticosteroids were

required in 1.1% of patients and high-dose corticosteroids was required in 0.4% patients with a median duration of 3 days (1 day to 11 days) followed by a corticosteroid taper.

The incidence of diarrhea or colitis in 793 TECENTRIQ-treated patients in IMpower150 was 27%, including Grade 3-4 (4.3%) events. Systemic corticosteroids were required in 4.5% of patients and high-dose corticosteroids was required in 3.2% patients with a median duration of 5 days (1 day to 103 days) followed by a corticosteroid taper.

5.4 Immune-Mediated Endocrinopathies

TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypopituitarism.

Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue TECENTRIQ for hypothyroidism and interrupt for hyperthyroidism based on the severity *[see Dosage and Administration (2.5)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ *[see Adverse Reactions (6.1)]*, hypothyroidism occurred in 4.6% of patients, and 3.8% of patients required the use of hormone replacement therapy. Hyperthyroidism occurred in 1.6% of patients. One patient experienced acute thyroiditis.

The incidence of hypothyroidism in 793 TECENTRIQ-treated patients in IMpower150 was 11.3%, and 8.6% of patients required hormone replacement therapy. Hyperthyroidism occurred in 3.4% of patients and 0.1% experienced thyroiditis.

Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper and hormone replacement as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.5)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (< 0.1%) adrenal insufficiency. Median time to onset was 5.7 months (3 days to 19 months). There was insufficient information to adequately characterize the median duration of adrenal insufficiency. Adrenal insufficiency resolved in 27% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids.

The incidence of adrenal insufficiency in 793 TECENTRIQ-treated patients in Study IMpower150 was 0.8%.

Type 1 *Diabetes Mellitus*: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.5)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, type 1 diabetes mellitus occurred in < 0.1% of patients. Insulin was required in one patient. The incidence of new onset diabetes mellitus in 698 TECENTRIQ-treated patients in Study IMpower150 was 0.1%

Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1–2 mg/kg/day or equivalents, followed by a taper and hormone replacement therapy as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.5)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, Grade 2 hypophysitis occurred in < 0.1% of patients.

The incidence of hypophysitis in 793 TECENTRIQ-treated patients in IMpower150 was 0.4%, including Grade 2 (0.1%) and Grade 3 (0.1%) events.

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 (2.5)]*.

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. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable *[see Dosage and Administration (2.5) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ *[see Adverse Reactions (6.1)]*, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients. In patients with NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients.

The incidence of infections in 793 TECENTRIQ-treated patients in IMpower150 was 50.1%, including Grade 3 (12%), Grade 4 (1.9%), and Grade 5 (0.4%). The most common Grade 3 or higher infection was pneumonia, occurring in 4.8% of patients.

5.7 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.5)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The incidence of infusion-related reactions in 793 TECENTRIQ-treated patients in IMpower150 was 3.8%, including Grade 3-4 (0.8%).

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in Warnings and Precautions reflect exposure to TECENTRIQ as a single agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types or in combination with paclitaxel and carboplatin with or without bevacizumab in 793 patients with metastatic non-squamous NSCLC from one randomized, open-label, active-controlled trial (IMpower150). TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Among 393 patients who received TECENTRIQ in

combination with bevacizumab, paclitaxel, and carboplatin and 400 patients who received TECENTRIQ in combination with paclitaxel and carboplatin in IMpower150, 65% and 54%, respectively, were exposed to TECENTRIQ for longer than 6 months and 36% and 28%, respectively, were exposed to TECENTRIQ for longer than 12 months.

The data described in this section were obtained from one open-label, single arm, multiple cohort study (IMvigor210) and two randomized open-label, active-controlled studies (OAK and IMpower150) in which TECENTRIQ was administered to 429 patients with locally advanced and metastatic urothelial carcinoma and 1002 patients with metastatic NSCLC. In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks. This section also describes data from one randomized, placebo-controlled study (IMpassion130) in which TECENTRIQ was administered (at a dose of 840 mg intravenously every 2 weeks) in combination with paclitaxel protein-bound to 452 patients with metastatic TNBC.

Locally Advanced or Metastatic Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor 210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

The most common adverse reactions (≥ 20%) were fatigue (52%), decreased appetite (24%), diarrhea (24%), and nausea (22%). The most common Grade 3–4 adverse reactions (≥ 2%) were fatigue, urinary tract infection, anemia, diarrhea, blood creatinine increase, intestinal obstruction, ALT increase, hyponatremia, decreased appetite, sepsis, back/neck pain, renal failure, and hypotension.

Five patients (4.2%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death. TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 3 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in IMvigor210 (Cohort 1).

Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[6]	17	0.8
Infections		
Urinary tract infection[7]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[8]	14	0
Dyspnea[9]	12	0

[1] Includes fatigue, asthenia, lethargy, and malaise
[2] Includes edema peripheral, scrotal edema, lymphedema, and edema
[3] Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
[4] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
[5] Includes decreased appetite and early satiety
[6] Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
[7] Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
[8] Includes cough and productive cough
[9] Includes dyspnea and exertional dyspnea

Table 3: Grade 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Laboratory Abnormality	Grades 3–4 (%)
Chemistry	

Laboratory Abnormality	Grades 3–4 (%)
Hyponatremia	15
Hyperglycemia	10
Increased Alkaline Phosphatase	7
Increased Creatinine	5
Hypophosphatemia	4
Increased ALT	4
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3
Hematology	
Lymphopenia	9
Anemia	7

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common adverse reactions (≥ 20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common Grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Table 4 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 5 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in IMvigor210 (Cohort 2).

statistically significant reduction in adverse reaction rates for TECENTRIQ, as compared to the control arm, for any specified adverse reaction or laboratory abnormality listed in Tables 6 and 7.

Table 6: Adverse Reactions Occurring in ≥15% of Patients Receiving TECENTRIQ in IMpower150

	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
Adverse Reaction	**All grades* (%)**	**Grade 3–4* (%)**	**All grades* (%)**	**Grade 3–4* (%)**
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

* Graded per NCI CTCAE v4.0

[1] includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy.

[2] includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform.

[3] includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, backpain, myalgia, and bone pain.

[4] includes diarrhea, gastroenteritis, colitis, enterocolitis.

[5] Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected.

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower150

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All grades %	Grade 3–4 %	All grades %	Grade 3–4 %
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA	44	NA
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA	20	NA
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	N/A	19	N/A
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13

NA = Not applicable. NCI CTCAE does not provide a Grade 3-4 definition for these laboratory abnormalities

Previously Treated Metastatic NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOG performance status of 1. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (44%), decreased appetite (24%), dyspnea (22%), and cough (26%). The most common Grade 3–4 adverse reactions (≥ 2%) were dyspnea, pneumonia, fatigue, and pulmonary embolism.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (> 1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain. Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (> 1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

Table 8 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ. Table 9 summarizes laboratory abnormalities worsening from baseline that occurred in ≥ 20% of patients treated with TECENTRIQ.

Table 8: 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 9: Laboratory Abnormalities Worsening From Baseline Occurring in ≥ 20% of NSCLC Patients Receiving TECENTRIQ in OAK

	TECENTRIQ 1200 mg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
Laboratory Abnormality	**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)

Metastatic Triple Negative Breast Cancer (TNBC)

The safety of TECENTRIQ in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blinded placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease [*see Clinical Studies (14.3)*]. Patients received 840 mg of TECENTRIQ (n=452) or placebo (n=438) intravenously followed by paclitaxel protein-bound (100 mg/m^2) intravenously. For each 28 day cycle, TECENTRIQ was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0-32 months) and paclitaxel protein-bound was 5.1 months (range: 0 – 31.5 months) in the TECENTRIQ plus paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0-23.7 months) in the placebo plus paclitaxel protein-bound arm.

The most common adverse reactions (≥20%) in patients receiving TECENTRIQ in combination with paclitaxel protein-bound were alopecia (56%), peripheral neuropathies (47%), fatigue (47%), nausea (46%), diarrhea (33%), anemia (28%), constipation (25%), cough (25%), headache (23%), neutropenia (21%), vomiting (20%), and decreased appetite (20%). The most common Grade 3-4 adverse reactions occurring in ≥2%, were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4.6%), fatigue (4%), anemia (2.9%), hypokalemia (2.2%), pneumonia (2.2%), and aspartate aminotransferase increased (2.0%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse

reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%). Fatal adverse reactions occurred in 1.3% (6/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism. Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (≥ 2%) were neutropenia, neutrophil count decreased, hyperthyroidism, and pyrexia. Serious adverse reactions occurred in 23% (103/452) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspnea (1%), and pyrexia (1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm.

Table 10 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ and paclitaxel protein-bound. Table 11 summarizes selected laboratory abnormalities worsening from baseline that occurred in at least 20% of patients in the TECENTRIQ treated patients.

Table 10: Adverse Reactions Occurring in ≥10% of Patients with TNBC (IMpassion130)

	TECENTRIQ in combination with paclitaxel protein-bound (n=452)		**Placebo in combination with paclitaxel protein-bound (n=438)**	
Adverse Reaction[1]	**All Grades (%)**	**Grade 3–4 (%)**	**All Grades (%)**	**Grade 3–4 (%)**
	Percentage (%) of Patients			
Skin and Subcutaneous Tissue Disorders				
Alopecia	56	<1	58	<1
Rash	17	<1	16	<1
Pruritus	14	0	10	0
General Disorders and administration site conditions				
Fatigue	47	4	45	3.4
Pyrexia	19	<1	11	0
Peripheral Edema	15	<1	16	1.4
Asthenia	12	<1	11	<1
Gastrointestinal Disorders				
Nausea	46	1.1	38	1.8
Diarrhea	33	1.3	34	2.1
Constipation	25	<1	25	<1
Vomiting	20	<1	17	1.1
Abdominal pain	10	<1	12	<1
Blood and Lymphatic System Disorders				
Anemia	28	2.9	26	3
Neutropenia	21	8	15	8
Investigations				
Neutrophil count decreased	13	4.6	11	3.4
Alanine aminotransferase increased	10	1.8	9	1.1
Nervous System Disorders				
Headache	23	<1	22	<1
Peripheral neuropathies[2]	47	9	44	5
Dysgeusia	14	0	14	0
Dizziness	14	0	11	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	25	0	19	0
Dyspnea	16	<1	15	<1
Metabolism and Nutrition Disorders				
Decreased Appetite	20	<1	18	<1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	<1	16	<1

Back pain	15	1.3	13	<1
Myalgia	14	<1	15	<1
Pain in extremity	11	<1	10	<1
Endocrine Disorders				
Hypothyroidism	14	0	3.4	0
Infections and infestations				
Urinary tract infection	12	<1	11	<1
Upper respiratory tract infection	11	1.1	9	0
Nasopharyngitis	11	0	8	0

[1] Graded per NCI CTCAE v4.0

[2] Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with TNBC (IMpassion130)

	Percentage of Patients with Worsening Laboratory Test from Baseline			
Laboratory Abnormality	**TECENTRIQ in combination with paclitaxel protein-bound (n=452)**		**Placebo in combination with paclitaxel protein-bound (n=438)**	
Test	**All Grades[1] (%)[2]**	**Grade 3–4 (%)**	**All Grades[1] (%)[2]**	**Grade 3–4 (%)**
Chemistry				
Increased Creatinine	21	<1	16	<1
Increased ALT	43	6	34	2.7
Increased AST	42	4.9	34	3.4
Decreased Calcium	28	1.1	26	<1
Decreased Sodium	27	4.2	25	2.7
Decreased Albumin	27	<1	25	<1
Increased Alkaline Phosphatase	25	3.3	22	2.7
Decreased Phosphate	22	3.6	19	3.7
Hematology				
Decreased Hemoglobin	79	3.8	73	3
Decreased Leukocytes	76	14	71	9
Decreased Neutrophils	58	13	54	13
Decreased Lymphocytes	54	13	47	8
Increased Prothrombin INR	25	<1	25	<1

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).

[2] Based on the number of patients with available baseline and at least one on-treatment laboratory test.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other atezolizumab products may be misleading.

Among 565 patients with NSCLC in OAK, 30% tested positive for treatment-emergent anti-drug antibodies (ADA) at one or more post-dose time points. The median onset time to ADA

formation was 3 weeks. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%; 118/560) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 *[see Clinical Studies (14.2)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 275 patients with urothelial carcinoma in IMvigor210 (Cohort 2), 42% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 111 patients in IMvigor210 (Cohort 1), 48% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposures. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 364 ADA-evaluable patients with NSCLC who received TECENTRIQ with bevacizumab, paclitaxel and carboplatin in IMpower150, (36% (n=132) tested positive for treatment-emergent ADA at one or more post-dose time points and 83% of these 132 patients tested ADA positive prior to receiving the second dose of atezolizumab. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA negative *[see Clinical Pharmacology (12.3)]*. The presence of ADA did not increase the incidence or severity of adverse reactions *[see Clinical Studies (14.2)]*.

Among 434 patients with TNBC in IMpassion130, 13% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 178 patients in PD-L1 positive subgroup with TNBC in IMpassion130, 12% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *(see Data).* Advise females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown

in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

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)]*.

Contraception

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

8.5 Geriatric Use

Of the 919 patients treated with TECENTRIQ as a single-agent in IMvigor210 (Cohort 2) and OAK, 50% were 65 years or older. Of the 400 patients randomized to TECENTRIQ in combination with bevacizumab, paclitaxel, and carboplatin in IMpower150, 46% were 65 years or older and 9% were 75 years or older. No overall differences in safety or efficacy were observed between patients 65 years or older and younger patients in IMvigor210 (Cohort 2), OAK, and IMpower150.

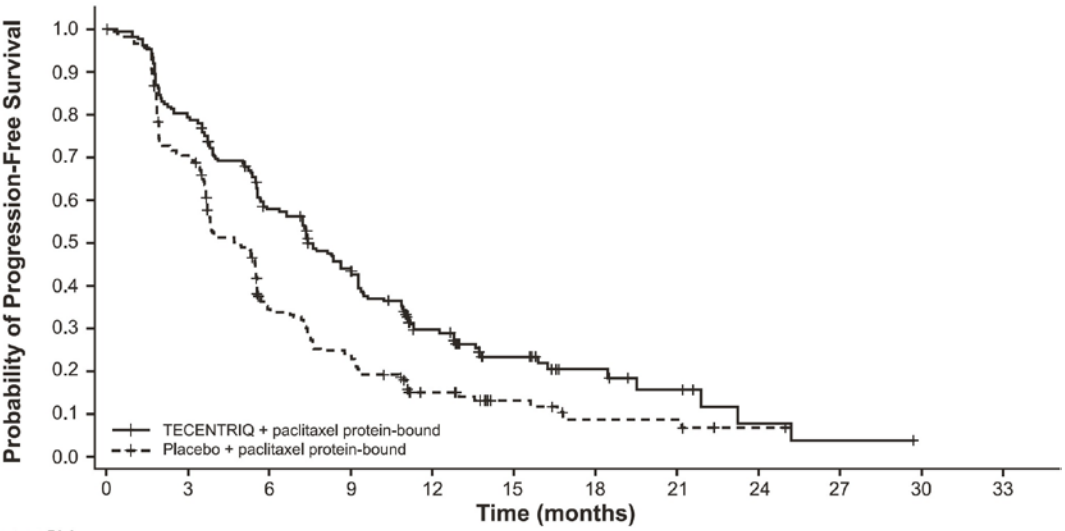
Of the 119 cisplatin-ineligible patients with urothelial carcinoma treated with TECENTRIQ as a single-agent in IMvigor210 (Cohort 1), 83% were 65 years or older and 41% were 75 years or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Of the 452 patients with TNBC treated with TECENTRIQ in combination with paclitaxel protein-bound in IMpassion130, 23% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Complete response (%)	17 (9)	1 (<1)
Partial response (%)	81 (44)	59 (32)
Duration of Response[2,3,6]	n=98	n=60
Median (months)	9.2	6.2
(95% CI)	(7.5, 11.9)	(5.5, 8.8)

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)
[2] As determined by investigator assessment
[3] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[4] Stratified by presence of liver metastases, and by prior taxane treatment
[5] patients with measurable disease at baseline
[6] confirmed responses
PFS=Progression-Free Survival; CI=Confidence Interval; ORR=Objective Response Rate; DOR=Duration of Response; NE=Not Estimable

Figure 3: Kaplan-Meier Plot of Progression-Free-Survival in IMpassion130 in Patients with PD-L1 Expression ≥1%



16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 840 mg/14 mL single-dose vial (NDC 50242-918-01) or 1200 mg/20 mL single-dose vial (NDC 50242-917-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.

- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.4)]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection *[see Warnings and Precautions (5.6)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
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South San Francisco, CA 94080-4990

U.S. License No. 1048

MEDICATION GUIDE
TECENTRIQ® (te-SEN-trik)
(atezolizumab)
injection

What is the most important information I should know about TECENTRIQ?

TECENTRIQ is a medicine that may treat certain cancers by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood or mucus in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the thyroid, adrenal glands, pancreas, and pituitary). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain

Problems in other organs. Signs and symptoms may include:

- severe muscle weakness
- numbness or tingling in hands or feet
- confusion
- blurry vision, double vision, or other vision problems
- changes in mood or behavior
- extreme sensitivity to light
- neck stiffness
- eye pain or redness
- skin blisters or peeling
- chest pain, irregular heartbeat, shortness of breath or swelling of the ankles

Severe infections. Signs and symptoms of infection may include:

- fever
- cough
- flu-like symptoms
- pain when urinating, frequent urination or back pain

Severe infusion reactions. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- swelling of your face or lips
- dizziness
- fever
- feeling like passing out
- back or neck pain

Getting medical treatment right away may help keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat adults with:

- **a type of bladder and urinary tract cancer called urothelial carcinoma.** TECENTRIQ may be used when your bladder cancer has spread or cannot be removed by surgery, **and if you have any one of the following conditions:**
  - you are not able to take chemotherapy that contains a medicine called cisplatin, and your cancer tests positive for "PD-L1", **or**
  - you are not able to take chemotherapy that contains any platinum regardless of "PD-L1" status, **or**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used with bevacizumab and the chemotherapy medicines carboplatin and paclitaxel as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type of lung cancer called "non-squamous NSCLC", **and**
    - your tumor does not have an abnormal "EGFR" or "ALK" gene.
  - **TECENTRIQ may be used when your lung cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working, **and**
    - if your tumor has an abnormal "EGFR" or "ALK" gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.
- **a type of breast cancer called triple-negative breast cancer (TNBC).** TECENTRIQ may be used with the medicine paclitaxel protein-bound when your breast cancer:
  - has spread or cannot be removed by surgery, **and**
  - your cancer tests positive for "PD-L1".

It is not known if TECENTRIQ is safe and effective in children.

Before you receive TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are being treated for an infection
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
  - You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.
- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 2 or 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of TECENTRIQ?

TECENTRIQ can cause serious side effects, including:

- **See "What is the most important information I should know about TECENTRIQ?"**

The most common side effects of TECENTRIQ when used alone include:

- feeling tired
- nausea
- constipation
- cough
- shortness of breath
- decreased appetite

The most common side effects of TECENTRIQ when used with bevacizumab, paclitaxel and carboplatin include:

- feeling tired or weak
- hair loss
- nausea
- diarrhea
- constipation
- decreased appetite
- joint pain
- high blood pressure
- tingling or numbness in hands and feet

The most common side effects of TECENTRIQ when used with paclitaxel protein-bound include:

- hair loss
- feeling tired
- tingling or numbness in hands and feet
- nausea
- diarrhea
- low red blood cells (anemia)
- constipation
- cough
- headache
- low white blood cells
- decreased appetite
- vomiting

TECENTRIQ may cause fertility problems in females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TECENTRIQ. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TECENTRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about TECENTRIQ, talk with your healthcare provider. You can ask your healthcare provider for information about TECENTRIQ that is written for health professionals.

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

Inactive ingredients: glacial acetic acid, L-histidine, polysorbate 20, and sucrose.

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 USA

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For more information, call 1-*844-832-3687* or go to www.TECENTRIQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 3/2019