HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KADCYLA safely and effectively. See full prescribing information for KADCYLA.

KADCYLA™ (ado-trastuzumab emtansine) for injection, for intravenous use
Initial U.S. Approval: 2013

WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not substitute KADCYLA for or with trastuzumab. (2.1)**
- **Hepatotoxicity, liver failure and death have occurred in KADCYLA-treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate. (2.2, 5.1)**
- **KADCYLA may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor and withhold dosing or discontinue as appropriate. (2.2, 5.2)**
- **Can cause fetal harm. Advise women of potential risk to the fetus. (5.3, 8.1, 8.6)**

RECENT MAJOR CHANGES
Dosage and Administration (2.3) 05/2013

INDICATIONS AND USAGE
KADCYLA is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy. (1)

DOSAGE AND ADMINISTRATION
- *For intravenous infusion only*. Do not administer as an intravenous push or bolus. Do not use Dextrose (5%) solution. (2.3)
- The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. *Do not administer KADCYLA at doses greater than 3.6 mg/kg. Do not substitute KADCYLA for or with trastuzumab.* (2.1)
- Management of adverse events (infusion-related reactions, hepatotoxicity, left ventricular cardiac dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy) may require temporary interruption, dose reduction, or treatment discontinuation of KADCYLA. (2.2)

DOSAGE FORMS AND STRENGTHS
Lyophilized powder in single-use vials containing 100 mg per vial or 160 mg per vial. (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
- Pulmonary Toxicity: Permanently discontinue KADCYLA in patients diagnosed with interstitial lung disease or pneumonitis. (2.2, 5.4)
- Infusion-Related Reactions, Hypersensitivity Reactions: Monitor for signs and symptoms during and after infusion. If significant infusion-related reactions or hypersensitivity reactions occur, slow or interrupt the infusion and administer appropriate medical therapies. Permanently discontinue KADCYLA for life threatening infusion-related reaction. (2.1, 2.2, 5.5)
- Thrombocytopenia: Monitor platelet counts prior to each KADCYLA dose. Institute dose modifications as appropriate. (2.2, 5.6)
- Neurotoxicity: Monitor for signs or symptoms. Withhold dosing temporarily for patients experiencing Grade 3 or 4 peripheral neuropathy. (2.2, 5.7, 13.2)
- HER2 Testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (5.8)

ADVERSE REACTIONS
The most common adverse drug reactions (frequency > 25%) with KADCYLA (n=884 treated patients) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. (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
- Nursing Mothers: Discontinue nursing or discontinue KADCYLA taking into consideration the importance of the drug to the mother. (8.3)
- Females of Reproductive Potential: Counsel females on pregnancy prevention and planning. Encourage patient participation in the MotHER Pregnancy Registry by contacting 1-800-690-6720). (5.3, 8.1, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

Do Not Substitute KADCYLA for or with Trastuzumab

WARNING: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

- Hepatotoxicity: Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin. (2.2, 5.1)
- Cardiac Toxicity: KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function. (2.2, 5.2)
- Embryo-Fetal Toxicity: Exposure to KADCYLA can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.6)

1 INDICATIONS AND USAGE

KADCYLA™, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Doses and Schedules

The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. *Do not administer KADCYLA at doses greater than 3.6 mg/kg*. *Do not substitute KADCYLA for or with trastuzumab.*

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration *[see Warnings and Precautions (5.9)]*.

First infusion: Administer infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions *[see Warnings and Precautions (5.5)]*.

Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after infusion.

2.2 Dose Modifications

KADCYLA dose should not be re-escalated after a dose reduction is made.

If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-

week interval between doses. The infusion may be administered at the dose and rate the patient tolerated in the most recent infusion.

The infusion rate of KADCYLA should be slowed or interrupted if the patient develops an infusion-related reaction. Permanently discontinue KADCYLA for life-threatening infusion-related reactions *[see Warnings and Precautions (5.5)]*.

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation of KADCYLA as per guidelines provided in Tables 1 to 5.

Table 1 Recommended Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Hepatotoxicity [see Warnings and Precautions (5.1)]

A reduction in the dose of KADCYLA is recommended in the case of hepatotoxicity exhibited as increases in serum transaminases and/or hyperbilirubinemia (see Tables 2 and 3).

Table 2 Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT)

Grade 2 (> 2.5 to ≤ 5 × ULN)	Grade 3 (> 5 to ≤ 20 × ULN)	Grade 4 (> 20 × ULN)
Treat at same dose level.	Do not administer KADCYLA until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level.	Permanently discontinue KADCYLA.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

Table 3 Dose Modification Guidelines for Hyperbilirubinemia

Grade 2 (> 1.5 to ≤ 3 × ULN)	Grade 3 (> 3 to ≤ 10 × ULN)	Grade 4 (> 10 × ULN)
Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1, and then reduce one dose level.	Permanently discontinue KADCYLA.

Permanently discontinue KADCYLA treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN.

Permanently discontinue KADCYLA in patients diagnosed with nodular regenerative hyperplasia (NRH).

Left Ventricular Dysfunction [see Warnings and Precautions (5.2)]

Table 4 Dose Modifications for Left Ventricular Dysfunction

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue KADCYLA	Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue KADCYLA.	Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue KADCYLA.	Continue treatment with KADCYLA. Repeat LVEF assessment within 3 weeks.	Continue treatment with KADCYLA.

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

Thrombocytopenia [see Warnings and Precautions (5.6)]

A reduction in dose is recommended in the case of Grade 4 thrombocytopenia (platelets < 25,000/mm^3) (see Table 5).

Table 5 Dose Modification Guidelines for Thrombocytopenia

Grade 3	Grade 4
PLT 25,000/mm^3 to < 50,000/mm^3	**PLT < 25,000/mm^3**
Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at same dose level.	Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.

PLT = Platelets

Pulmonary Toxicity [see Warnings and Precautions (5.4)]

KADCYLA should be permanently discontinued in patients diagnosed with interstitial lung disease (ILD) or pneumonitis.

Peripheral Neuropathy [see Warnings and Precautions (5.7)]

KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2.

2.3 Preparation for Administration

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is KADCYLA (ado-trastuzumab emtansine) and not trastuzumab.

Administration:

- Administer KADCYLA as an intravenous infusion only with a 0.22 micron in-line polyethersulfone (PES) filter. Do not administer as an intravenous push or bolus.
- Do not mix KADCYLA, or administer as an infusion, with other medicinal products.
- In order to improve traceability of biological medicinal products, the tradename of the administered product should be clearly recorded (or stated) in the patient file.

Reconstitution:

- Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.
- Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg KADCYLA vial, or 8 mL of Sterile Water for Injection into the 160 mg KADCYLA vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. *Do not shake.* Inspect the reconstituted solution for particulates and discoloration.
- The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.
- The reconstituted lyophilized vials should be used immediately following reconstitution with Sterile Water for Injection. If not used immediately, the reconstituted KADCYLA vials can be stored for up to 24 hours in a refrigerator at 2ºC to 8ºC (36°F to 46°F); discard unused KADCYLA after 24 hours. *Do not freeze.*
- The reconstituted product contains no preservative and is intended for single-use only.

Dilution:

Determine the correct dose (mg) of KADCYLA *[see Dosage and Administration (2.1)]*.

- Calculate the volume of the 20 mg/mL reconstituted KADCYLA solution needed.
- Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. *Do not use Dextrose (5%) solution.*
- Gently invert the bag to mix the solution in order to avoid foaming.
- The diluted KADCYLA infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use. This storage time is additional to the time allowed for the reconstituted vials. *Do not freeze or shake.*

3 DOSAGE FORMS AND STRENGTHS

Lyophilized powder in single-use vials: 100 mg per vial or 160 mg per vial of ado-trastuzumab emtansine.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic, transient increases in the concentrations of serum transaminases, has been observed in clinical trials with KADCYLA *[see Adverse Reactions (6.1)]*. Serious hepatobiliary disorders, including at least two fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in

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