

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrKADCYLA®**

trastuzumab emtansine for injection

100 mg and 160 mg, sterile powder, intravenous infusion only

Antineoplastic Agent

Hoffmann-La Roche Limited  
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Mississauga, Ontario, Canada  
L5N 5M8

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## RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	09/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

#### Metastatic Breast Cancer (MBC)

Kadcyla (trastuzumab emtansine for injection) monotherapy is indicated for the treatment of HER2-positive metastatic breast cancer patients who received both prior treatment with 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 6 months of completing adjuvant therapy.

#### Early Breast Cancer (EBC)

Kadcyla monotherapy is indicated for the adjuvant treatment of HER2-positive early breast cancer patients who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment.

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (> 65 age):** No dose adjustment of the Kadcyla starting dose is required in patients aged > 65 to < 75 years of age. There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.4 Geriatrics).

### 2 CONTRAINDICATIONS

Kadcyla is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

- **There is a risk of medication errors between Kadcyła (trastuzumab emtansine for injection) and trastuzumab. In order to minimize this risk, check the vial labels to ensure that the drug being prepared and administered is Kadcyła (trastuzumab emtansine for injection) and not trastuzumab. Kadcyła should be prescribed using both the trade name and non-proprietary name (see 4 DOSAGE AND ADMINISTRATION: 4.1 Dosing Considerations).**
- **Liver Toxicity:** Hepatotoxicity, liver failure and death have occurred in Kadcyła-treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate (see 7 WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).
- **Cardiotoxicity:** Kadcyła may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF prior to initiation. Monitor during treatment and withhold dosing or discontinue as appropriate (see 7 WARNINGS AND PRECAUTIONS: Cardiovascular).
- **Hemorrhage:** Fatal cases of hemorrhage occurred in clinical trials among patients with no known identified risk factors, as well as among patients with thrombocytopenia and those receiving anti-coagulation and antiplatelet therapy. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary (see 7 WARNINGS AND PRECAUTIONS: Hematologic)
- **Interstitial lung disease (ILD):** Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with Kadcyła. It is recommended that treatment with Kadcyła be permanently discontinued in patients who are diagnosed with ILD or pneumonitis (see 7 WARNINGS AND PRECAUTIONS: Respiratory).
- **Embryo-fetal Toxicity:** Kadcyła can cause fetal harm or death of the fetus. Advise women of potential risk to the fetus (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.1 Pregnant Women).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

Kadcyła should only be used in patients with HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of  $\geq 2.0$  by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a validated test in an accredited laboratory.

There is a risk of medication errors between Kadcyła (trastuzumab emtansine) and trastuzumab. In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Kadcyła (trastuzumab emtansine for injection) and not trastuzumab. Ensure that the recommended Kadcyła dose is administered (see 4 DOSAGE AND ADMINISTRATION). These will avoid overdose and toxicity (see 5 OVERDOSAGE).

Kadcyła should only be administered under the supervision of a health professional experienced in the treatment of cancer patients.

Kadcyla must be reconstituted and diluted by an appropriately trained health professional. Kadcyla should be administered as an intravenous infusion (see 4 DOSAGE AND ADMINISTRATION: 4.4 Administration). Do not administer as an intravenous push or bolus.

## 4.2 Recommended Dose and Dosage Adjustment

### Recommended Dose:

The recommended starting dose of Kadcyla is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle). Do not administer Kadcyla at doses > 3.6 mg/kg.

Patients with early breast cancer (EBC) should receive Kadcyla for 14 cycles or until there is disease progression or unmanageable toxicity.

Patients with metastatic breast cancer (MBC) should receive Kadcyla until disease progression or unmanageable toxicity.

Administer the initial Kadcyla dose of 3.6 mg/kg as a 90-minute intravenous infusion. 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. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration (see 7 WARNINGS AND PRECAUTIONS: Extravasation).

If prior infusions were well tolerated, subsequent doses of Kadcyla may be administered as 30-minute infusions and patients should be observed during the infusions and for at least 30 minutes after infusion.

The infusion rate of Kadcyla should be slowed or interrupted if the patient develops infusion-related symptoms (see 7 WARNINGS AND PRECAUTIONS: Infusion-Related Reactions, Hypersensitivity Reactions). Permanently discontinue Kadcyla for life-threatening infusion reactions.

### Dose Adjustment:

Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided in Table 1, Table 2 and Table 3.

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

**Table 1 Dose Reduction Schedule**

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3.0 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Permanently discontinue treatment

**Table 2 Dose Modification Guidelines for Kadcyła Patients with MBC**

<b>Adverse Reaction</b>	<b>Severity</b>	<b>Treatment Modification</b>
Increased Transaminase (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× the ULN)	Treat at the same dose level
	Grade 3 (> 5 to ≤ 20× the ULN)	Do not administer Kadcyła until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level
	Grade 4 (> 20× the ULN)	Permanently discontinue Kadcyła
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× the ULN)	Do not administer Kadcyła until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.
	Grade 3 (> 3 to ≤ 10× the ULN)	Do not administer Kadcyła until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10× the ULN)	Permanently discontinue Kadcyła
Drug Induced Liver Injury (DILI)	Serum transaminases > 3× ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue Kadcyła in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyła
Thrombocytopenia	Grade 3 (25,000 to < 50,000/mm <sup>3</sup> )	Do not administer Kadcyła until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm <sup>3</sup> ), and then treat at the same dose level
	Grade 4 (< 25,000/mm <sup>3</sup> )	Do not administer Kadcyła until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm <sup>3</sup> ), and then reduce one dose level
Left Ventricular Dysfunction	Symptomatic CHF	Permanently discontinue Kadcyła
	LVEF <40%	Do not administer Kadcyła Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, permanently discontinue Kadcyła
	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer Kadcyła Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, permanently discontinue Kadcyła
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with Kadcyła. Repeat LVEF assessment within 3 weeks.

Adverse Reaction	Severity	Treatment Modification
	LVEF > 45%	Continue treatment with Kadcyła.
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyła
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyła until resolution ≤ Grade 2

**Table 3 Dose Modification Guidelines for Kadcyła Patients with EBC**

Adverse Reaction	Severity	Treatment Modification
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20× ULN on day of scheduled treatment)	Do not administer Kadcyła until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20× ULN at any time)	Permanently discontinue Kadcyła
Increased Aspartate Transaminase (AST)	Grade 2 (> 3 to ≤ 5× ULN on day of scheduled treatment)	Do not administer Kadcyła until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20× ULN on day of scheduled treatment)	Do not administer Kadcyła until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20× ULN at any time)	Permanently discontinue Kadcyła
Hyperbilirubinemia	TBILI > 1 to ≤ 2× the ULN on day of scheduled treatment	Do not administer Kadcyła until total bilirubin recovers to ≤ 1.0× ULN, and then reduce one dose level
	TBILI > 2× ULN at any time	Permanently discontinue Kadcyła
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyła
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to < 75,000/mm <sup>3</sup> )	Do not administer Kadcyła until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm <sup>3</sup> ), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time < 25,000/mm <sup>3</sup>	Do not administer Kadcyła until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm <sup>3</sup> ), and then reduce one dose level.
Left Ventricular Dysfunction	LVEF < 45%	Do not administer Kadcyła Repeat LVEF assessment within 3 weeks. If

Adverse Reaction	Severity	Treatment Modification
		LVEF < 45% is confirmed, permanently discontinue Kadcyła.
	LVEF 45% to < 50% and decrease is $\geq$ 10% points from baseline*	Do not administer Kadcyła Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, permanently discontinue Kadcyła.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with Kadcyła. Repeat LVEF assessment within 3 weeks.
	LVEF $\geq$ 50%	Continue treatment with Kadcyła.
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Permanently discontinue Kadcyła
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyła until resolution $\leq$ Grade 2
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyła
Radiotherapy-Related Pneumonitis	Grade 2	Permanently discontinue Kadcyła if not resolving with standard treatment
	Grade 3-4	Permanently discontinue Kadcyła

ALT = alanine transaminase, AST = aspartate transaminase, CHF = congestive heart failure, DILI = Drug Induced Liver Injury, LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = Total Bilirubin, ULN = upper limit of normal

\*Prior to starting Kadcyła treatment.

**Pediatric Use (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.3 Pediatrics).

**Geriatric Use (> 65 years of age):** No adjustment to the starting dose of Kadcyła is required in patients aged > 65 to < 75 years of age. There are limited number of patients  $\geq$  75 years of age enrolled into clinical trials with Kadcyła (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.4 Geriatrics).

**Renal Impairment:** No adjustment to the starting dose of Kadcyła is recommended in patients with mild or moderate renal impairment (see 10 CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency). The potential

need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data.

**Hepatic Impairment:** No adjustment to the starting dose of Kadcyla is recommended in patients with mild or moderate hepatic impairment despite lower overall exposure of trastuzumab emtansine in these patients (see 10 CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency). Kadcyla has not been studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with Kadcyla (see 7 WARNINGS AND PRECAUTIONS: Hepatotoxicity).

### 4.3 Reconstitution

Vial Size	Volume of Diluent to be Added to the Vial	Nominal Concentration per mL
100 mg	5 mL Sterile Water	20 mg per mL
160 mg	8 mL Sterile Water	20 mg per mL

- Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg vial, or 8 mL of Sterile Water for Injection into the 160 mg Kadcyla vial.
- Swirl the vial gently until completely dissolved. DO NOT SHAKE!
- Store reconstituted Kadcyla at 2-8°C; discard unused Kadcyla after 24 hours.

#### Instructions for dilution:

Determine the volume of the solution required based on the dose to be administered. The standard dose is 3.6 mg Kadcyla/kg body weight; however, reduced doses may be required to manage certain toxicities (see Tables 2 and 3):

$$\text{Volume (mL)} = [\text{Body weight (kg)} \times \text{dose (mg/kg)}] / 20 \text{ mg/mL (concentration of reconstituted solution)}$$

The appropriate amount of solution should be withdrawn from one or more vials and added to an infusion bag containing 250 mL of 0.45% sodium chloride or 0.9% sodium chloride. Choose the appropriate vial sizes to minimize the amount of Kadcyla that is discarded.

Dextrose (5%) solution should not be used. 0.45% sodium chloride may be used without a 0.2-micron in-line (non-protein adsorptive)/0.22 micron polyethersulfone (PES) filter. If 0.9% sodium chloride is used for infusion, a 0.2-micron in-line (non-protein adsorptive)/ 0.22 micron polyethersulfone (PES) filter is required. Once the infusion is prepared, it should be administered immediately. If not used immediately, the infusion can be stored for up to 24 hours in a refrigerator at 2-8°C. The infusion cannot be frozen or shaken during storage.

#### Incompatibilities:

Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Kadcyla should not be mixed or diluted with other drugs.

### 4.4 Administration

Appropriate aseptic technique should be used. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion.

Reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution should be free of visible particulates, clear to slightly opalescent. The colour of the reconstituted solution should be colourless to pale brown. Do not administer if reconstituted solution contains visible particulates, or is cloudy or discoloured.

#### 4.5 Missed Dose

If a planned dose of Kadcyła is missed, it should be administered as soon as possible as per clinical judgment. Do not wait until the next planned cycle if clinically appropriate. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the rate the patient tolerated the most recent infusion.

### 5 OVERDOSAGE

There is a risk of Kadcyła overdose due to medication errors. Ensure that the authorized Kadcyła (trastuzumab emtansine for injection) dose and NOT trastuzumab dose is administered.

For management of a suspected drug overdose, contact your regional poison control centre.

There is no known antidote for Kadcyła overdose. In case of overdose, the patient should be closely monitored. Cases of overdose have been reported with Kadcyła treatment, most associated with thrombocytopenia, and there was one death. In the fatal case, the patient incorrectly received Kadcyła 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to Kadcyła were unknown.

### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 4 Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous (IV) infusion	100 mg single-use vial	polysorbate 20, sodium hydroxide, succinic acid, and sucrose.
	160 mg single-use vial	

100 mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 5 mL of 20 mg/mL of trastuzumab emtansine.

160 mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 8 mL of 20 mg/mL of trastuzumab emtansine.

## 7 WARNINGS AND PRECAUTIONS

### General

Kadcyla should only be prescribed and initiated by health professionals experienced with cancer therapeutic drugs.

Kadcyla should be prescribed using both the trade name and non-proprietary name. In order to improve traceability of biological medicinal products, the trade name and the lot number of the administered product should be clearly recorded (or stated) in the patient file.

### Cardiovascular

#### Left Ventricular Dysfunction

Patients treated with Kadcyla are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with Kadcyla, and therefore symptomatic congestive heart failure (CHF) is a potential risk. Across metastatic breast cancer (MBC) and early breast cancer (EBC) clinical trials, left ventricular dysfunction occurred in the Kadcyla-treated patients. Long-term effects of Kadcyla on cardiotoxicity is unknown (see 8 ADVERSE REACTIONS).

Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed prior to initiation and at regular intervals (e.g. every three months) during treatment with Kadcyla. Dosing reductions or permanent discontinuation of Kadcyla therapy may be required (see 4 DOSAGE AND ADMINISTRATION: 4.2 Recommended Dose and Dosage Adjustment). Evaluation of cardiac function following treatment discontinuation, in particular for patients with pre-existing cardiac dysfunction or with LVEF decline, should be considered and ordered based upon clinician judgment.

Treatment with Kadcyla has not been studied in patients with LVEF <50% prior to initiation of treatment in clinical trials.

Safety information were obtained from an observational study (BO3987) in a real world setting where 32 patients with MBC who had baseline LVEF of 40-49% were treated with Kadcyla. CHF were observed in 5 patients (15.6%; 5/32) and 4 out of 24 (16.7%) patients who had a post-treatment LVEF value experienced a decrease of LVEF >10%. Among these 9 patients, 2 had both CHF and a decrease of LVEF >10%. Most patients in the study had other cardiovascular risk factors. The decision to administer Kadcyla in patients with MBC with low LVEF must be made only after careful benefit risk assessment and cardiac function should be closely monitored in these patients.

### Driving and Operating Machinery

Kadcyla may impair the ability to drive and use machines as adverse reactions including fatigue, headache, dizziness and blurred vision have been reported. Patients experiencing infusion-related reactions (flushing, shivering fits, trouble breathing, low blood pressure or rapid heartbeat) should be advised not to drive and use machines until symptoms abate.

## Hematologic

### Hemorrhage

Bleeding events with fatal outcomes have occurred. Severe cases of hemorrhagic events, including central nervous system, respiratory and gastrointestinal hemorrhage, have been reported with Kadcyła. In some of the cases, there were no known additional risk factors, while in others the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia. Caution is advised and additional monitoring is recommended when Kadcyła is administered to patients who have decreased platelet counts or who require anti-coagulation or antiplatelet therapies.

In EBC, the incidence of hemorrhage events with trastuzumab emtansine was moderately higher in Asian patients (37.5% vs 28.4%), while the incidence of severe (Grade  $\geq 3$ ) hemorrhage events and serious hemorrhage events with trastuzumab emtansine was very low irrespective of the race, with occurrence limited to a single Asian patient. In the MBC population, the incidence of hemorrhages was similar in Asian and in non-Asian patients. This includes severe (Grade  $\geq 3$ ), serious and fatal hemorrhages, where no difference between Asian and non-Asian patients was noted.

### Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was commonly reported in patients in clinical trials of Kadcyła. An increase in the incidence and severity of thrombocytopenia has been observed in Asian patients treated with Kadcyła vs. non-Asian patients. In the pivotal EBC study,  $\geq$  Grade 3 thrombocytopenia occurred in 12 of 64 Asian patients (18.8%) and in 30 of 676 (4.4%) non-Asian patients treated with Kadcyła and serious adverse events of thrombocytopenia occurred in 5 of 64 (7.8%) Asian patients and in 5 of 676 (0.7%) non-Asian patients.

Patients with thrombocytopenia ( $<100,000/\text{mm}^3$ ) and patients on anti-coagulation treatment should be monitored closely while on Kadcyła treatment. Platelet counts should be monitored prior to each Kadcyła dose. Kadcyła has not been studied in patients with platelet counts  $<100,000/\text{mm}^3$  prior to initiation of treatment.

For patients with EBC, in the event of decreased platelet counts to  $\geq$  Grade 2 ( $<75,000/\text{mm}^3$ ), do not administer Kadcyła until platelet counts recover to Grade 1 ( $\geq 75,000/\text{mm}^3$ ). For patients with MBC, in the event of decreased platelet count to  $\geq$  Grade 3 ( $<50,000/\text{mm}^3$ ), do not administer Kadcyła until platelet counts recover to Grade 1 ( $\geq 75,000/\text{mm}^3$ ) (see 4 DOSAGE AND ADMINISTRATION: 4.2 Recommended Dose and Dosage Adjustment).

## Hepatic/Biliary/Pancreatic

### Hepatotoxicity

Treatment of patients with hepatic impairment should be undertaken with caution and with increased monitoring of liver function due to known hepatotoxicity observed with Kadcyła.

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), have occurred with Kadcyła treatment in clinical trials (see 8 ADVERSE REACTIONS: Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). In patients with MBC, transaminase elevations were generally transient with peak elevation at day 8 after therapy and subsequent

recovery to Grade 1 or less prior to the next cycle. A cumulative effect of Kadcyła on transaminases has been observed. MBC patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of Kadcyła in the majority of the cases.

Serious hepatobiliary disorders, including fatalities, have been reported including severe drug induced liver injury (with hepatic encephalopathy) and liver failure associated with nodular regenerative hyperplasia (NRH) of the liver. Cases of NRH have been observed in Kadcyła treated patients enrolled in clinical trials of both MBC and EBC. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can be confirmed only by histopathology. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver but with normal transaminases and no other manifestations of cirrhosis. Upon diagnosis of NRH, Kadcyła treatment must be permanently discontinued.

Liver function should be monitored prior to initiation of treatment and prior to each Kadcyła dose. Dose reductions or discontinuations for increased serum transaminases and total bilirubin are specified in 4 DOSAGE AND ADMINISTRATION: 4.2 Recommended Dose and Dosage Adjustment.

Kadcyła has not been studied in patients with serum transaminases > 2.5x ULN or total bilirubin > 1.5x ULN prior to initiation of treatment in MBC or in patients with serum transaminases > 1.5x ULN or total bilirubin > 1.0x ULN prior to initiation of treatment in EBC. Kadcyła treatment should be permanently discontinued in patients with serum transaminases > 3x ULN and concomitant total bilirubin > 2x ULN.

## **Immune**

### Infusion-Related Reactions

Treatment with Kadcyła has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRRs); treatment with Kadcyła is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of Kadcyła. In most patients, these reactions were ≤ Grade 2 and resolved over the course of several hours to a day after the infusion was terminated. Patients should be observed closely for IRRs, especially during the first infusion. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Kadcyła treatment should be interrupted in patients with severe IRR (≥Grade 3). Kadcyła treatment should be permanently discontinued in the event of a life-threatening IRR (see 4 DOSAGE AND ADMINISTRATION: 4.2 Recommended Dose and Dosage Adjustment).

### Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first infusion. Hypersensitivity, including serious, anaphylactic-like reactions, has been observed in clinical trials with treatment of Kadcyła. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

## Monitoring and Laboratory Tests

### Selection of Patients/Diagnostic Tests

Kadcyla should only be used in patients with HER2 positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of  $\geq 2.0$  by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a validated test.

### Monitoring

Patients should be assessed prior to starting Kadcyla and monitored throughout treatment with the following assessments. Test results should be within guidelines presented in Tables 1, 2 and 3 found in Section 4.2 of this Product Monograph prior to dosing with appropriate changes to the dosing regimen if required.

Prior to each dose (or if clinically indicated):

- Pregnancy test (if applicable)
- Liver function tests: ALT, AST, total bilirubin
- Hematology: CBC (platelet count)

Every 3 months (or as clinically indicated):

- Left ventricular ejection fraction: either echocardiogram or MUGA

## Neurologic

### Neurotoxicity

Peripheral neuropathy, predominantly sensory (e.g. numbness, tingling, pain, crawling sensation, pins and needles in hands and feet), has been reported in clinical trials of Kadcyla. Treatment with Kadcyla should be withheld in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to  $\leq$  Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

## Reproductive Health: Female and Male Potential

Women of child bearing potential and male partners of female patients of childbearing potential should use at least two effective contraception methods while receiving Kadcyla and for at least 7 months following the last dose of Kadcyla. If pregnancy occurs, the physician should be immediately informed.

- Fertility  
No dedicated fertility studies have been conducted with trastuzumab emtansine. However, based on results from animal toxicity studies, Kadcyla may impair fertility in females and males of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY: Reproductive and Developmental Toxicology).
- Teratogenic Risk  
Dedicated embryo-fetal development studies have not been conducted with trastuzumab emtansine (see 16 NON-CLINICAL TOXICOLOGY: Reproductive and Developmental Toxicology). However, Kadcyla can cause fetal harm or death when administered to a pregnant woman (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.1 Pregnant Women).

## Respiratory

### Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with Kadcyła. In MBC, ILD reported as pneumonitis had an incidence of 0.8% (7 out of 884), with one Grade 3 case reported as pneumonitis and one case of Grade 2 pneumonitis which later resulted in Grade 4 Acute Respiratory Distress Syndrome (ARDS) upon rechallenge with Kadcyła. In EBC, pneumonitis was reported at an incidence of 1.1% (8 out of 740 patients treated with KADCYLA), with one case (0.1%) of Grade 3 pneumonitis (see 8 ADVERSE REACTIONS). Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as part of an infusion-related reaction.

Kadcyła may also increase the risk of radiation pneumonitis in EBC patients receiving radiation therapy as part of adjuvant therapy. In the pivotal EBC trial, radiation pneumonitis was reported at an incidence of 1.8% in Kadcyła treated patients who received radiation therapy (11 out of 623), with two cases of Grade 3 radiation pneumonitis (see 8 ADVERSE REACTIONS).

It is recommended that treatment with Kadcyła be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant EBC setting, where Kadcyła should only be permanently discontinued for  $\geq$  Grade 3 events or when Grade 2 events do not respond to standard treatment (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

Patients with dyspnea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of pulmonary events when treated with Kadcyła.

### **Skin (Local) Reactions at Administration Sites**

#### Extravasation

In Kadcyła clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. In the post marketing setting, a few serious cases of epidermal injury or necrosis following extravasation have been observed within a few days after infusion and comprised burning sensation, ulcerative injury, blistering and skin necrosis. Specific treatment for Kadcyła extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

Kadcyła can cause fetal harm or death when administered to a pregnant woman. No clinical studies of Kadcyła in pregnant women have been performed. No reproductive and developmental toxicology studies have been conducted with Kadcyła.

However, in the post-marketing setting, some pregnant women receiving trastuzumab, the antibody component of Kadcyła, developed oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. In addition, the mechanism of action of DM1, the microtubule inhibiting cytotoxic drug component of Kadcyła, suggest that DM1 can cause teratogenicity and embryotoxicity.

Kadcyła should not be administered to pregnant women. Women who become pregnant must contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Kadcyła, close monitoring by a multidisciplinary team is recommended.

The safe use of Kadcyła during labor and delivery has not been established.

### 7.1.2 Breast-feeding

It is not known whether Kadcyła is excreted in human breast milk. A study conducted in lactating cynomolgus monkeys demonstrated that trastuzumab was secreted in the milk. As human IgG is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Kadcyła, women should discontinue nursing prior to initiating treatment with Kadcyła. Women may begin nursing 7 months following last dose of Kadcyła after concluding treatment.

### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

**Geriatrics (≥ 65 to < 75 years of age):** Of 495 patients who were randomized to Kadcyła in the pivotal metastatic breast cancer (MBC) study, 65 patients (13%) were ≥ 65 to < 75 years of age. Of the 743 patients who were randomized to Kadcyła in the pivotal EBC study, 58 patients (8%) were ≥ 65 to < 75 years of age. No overall differences in the safety or effectiveness of Kadcyła were observed in patients aged ≥ 65 to < 75 years of age compared to patients < 65 years of age in the MBC or EBC studies.

**Geriatrics (≥ 75 years of age):** Only eleven patients (2%) in the pivotal MBC study were ≥ 75 years of age and only two patients (0.3%) in the pivotal EBC study were ≥ 75 years of age. There are insufficient data to establish the safety and efficacy of Kadcyła in patients 75 years of age or older.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The most common adverse reactions (≥ 10%) with Kadcyła in MBC were nausea, musculoskeletal pain, fatigue, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, diarrhea, epistaxis, anemia, peripheral neuropathy, arthralgia, vomiting, pyrexia, abdominal pain, cough, asthenia, dry mouth, myalgia, stomatitis, insomnia, rash, dyspnea, urinary tract infection, dizziness, and hypokalemia.

The most common adverse reactions (≥ 10%) with Kadcyła in EBC were fatigue, nausea, increased transaminases, musculoskeletal pain, hemorrhage, thrombocytopenia, headache,

peripheral neuropathy, arthralgia, epistaxis, constipation, myalgia, stomatitis, vomiting, insomnia, dry mouth, cough, diarrhea, abdominal pain, pyrexia, urinary tract infection, and anemia.

The most common serious adverse reactions ( $\geq 1\%$ ) with Kadcyła in MBC were vomiting and pyrexia. The most common serious adverse reactions ( $\geq 1\%$ ) with Kadcyła in EBC were mastitis and thrombocytopenia.

Deaths have occurred in clinical studies with Kadcyła (see later in this section, Additional Information on Selected Adverse Reactions). Dose modification guidelines for Kadcyła patients with increased transaminases, hyperbilirubinemia, drug induced liver injury, nodular regenerative hyperplasia, thrombocytopenia, left ventricular dysfunction, heart failure, peripheral neuropathy, pulmonary toxicity, and radiotherapy related pneumonitis are described (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

## 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

### Metastatic Breast Cancer

The safety of Kadcyła (trastuzumab emtansine) has been evaluated in more than 880 patients in clinical trials. Table 5 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Kadcyła in the pivotal study TDM4370g/BO21977 (EMILIA). Table 7 summarizes the adverse reactions that have been reported in association with the use of Kadcyła across MBC clinical trials.

**Table 5 Summary of ADRs Occurring in  $\geq 1\%$  of Patients on the Kadcyła Treatment Arm in the Randomized Study TDM4370g/BO21977 (EMILIA)**

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyła (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m <sup>2</sup> ) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
<b>Blood and Lymphatic System Disorders</b>				
Thrombocytopenia	154 (31.4)	73 (14.9)	16 (3.3)	2 (0.4)
Anemia	72 (14.7)	22 (4.5)	51 (10.5)	12 (2.5)
Neutropenia	37 (7.6)	11 (2.2)	53 (10.9)	22 (4.5)
Leukopenia	21 (4.3)	5 (1.0)	23 (4.7)	6 (1.2)
<b>Cardiac Disorders</b>				
Left ventricular dysfunction	10 (2.0)	1 (0.2)	16 (3.3)	2 (0.4)
<b>Eye Disorders</b>				
Vision blurred	22 (4.5)	0	4 (0.8)	0
Conjunctivitis	20 (4.1)	0	11 (2.3)	0

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m <sup>2</sup> ) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Dry eye	20 (4.1)	0	15 (3.1)	0
Lacrimation increased	16 (3.3)	0	12 (2.5)	0
<b>Gastrointestinal Disorders</b>				
Nausea	196 (40.0)	4 (0.8)	221 (45.3)	12 (2.5)
Constipation	131 (26.7)	2 (0.4)	55 (11.3)	0.0
Diarrhea	122 (24.9)	9 (1.8)	390 (79.9)	102 (20.9)
Vomiting	94 (19.2)	4 (0.8)	146 (29.9)	22 (4.5)
Abdominal pain	91 (18.6)	4 (0.8)	86 (17.6)	8 (1.6)
Dry Mouth	82 (16.7)	0	24 (4.9)	1 (0.2)
Stomatitis	69 (14.1)	1 (0.2)	160 (32.8)	12 (2.4)
Dyspepsia	45 (9.2)	0	56 (11.5)	2 (0.4)
Gingival bleeding	21 (4.3)	0	7 (1.4)	0
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	179 (36.5)	12 (2.4)	138(28.3)	17 (3.5)
Pyrexia	91 (18.6)	1 (0.2)	41 (8.4)	2 (0.4)
Asthenia	88 (18.0)	2 (0.4)	87 (17.8)	8 (1.6)
Chills	38 (7.8)	0	15 (3.1)	0
Peripheral edema	35 (7.1)	0	40 (8.2)	1 (0.2)
<b>Immune System Disorders</b>				
Drug hypersensitivity	11 (2.2)	0	4 (0.8)	0
<b>Infections and Infestations</b>				
Urinary tract infection	58 (11.8)	3 (0.6)	24 (4.9)	0
<b>Injury, Poisoning, and Procedural Complications</b>				
Infusion-related reaction	7 (1.4)	0	1 (0.2)	0
<b>Investigations</b>				
Increased transaminases	141 (28.8)	39 (8.0)	70 (14.3)	12 (2.5)
Blood alkaline phosphatase increased	23 (4.7)	2 (0.4)	18 (3.7)	2 (0.4)
<b>Metabolism and Nutrition Disorders</b>				
Hypokalemia	50 (10.2)	13 (2.7)	48 (9.8)	23 (4.7)
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal pain	182 (37.1)	9 (1.8)	150 (30.7)	7 (1.4)
Arthralgia	96 (19.6)	3 (0.6)	43 (8.8)	0
Myalgia	69 (14.1)	3 (0.6)	18 (3.7)	0
<b>Nervous System Disorders</b>				
Headache	140 (28.6)	4 (0.8)	72 (14.8)	4 (0.8)
Peripheral neuropathy	106 (21.6)	12 (2.4)	66 (13.5)	1 (0.2)
Dizziness	52 (10.6)	2 (0.4)	53 (10.9)	1 (0.2)
Dysgeusia	40 (8.2)	0	20 (4.1)	1 (0.2)
<b>Psychiatric Disorders</b>				
Insomnia	60 (12.2)	2 (0.4)	43 (8.8)	1 (0.2)

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=490 Frequency %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m <sup>2</sup> ) n=488 Frequency %	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Epistaxis	113 (23.1)	1 (0.2)	41 (8.4)	0
Cough	90 (18.4)	1 (0.2)	64 (13.1)	1 (0.2)
Dyspnea	58 (11.8)	4 (0.8)	39 (8.0)	2 (0.4)
Pneumonitis	6 (1.2)	0	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	58 (11.8)	0	134 (27.5)	10 (2.0)
Pruritus	27 (5.5)	1 (0.2)	46 (9.4)	0
Alopecia	17 (3.5)	0	22 (4.5)	0
Nail disorder	14 (2.9)	0	45 (9.2)	3 (0.6)
Palmar-plantar erythrodysesthesia syndrome	7 (1.4)	0	288 (59.0)	86 (17.6)
Urticaria	5 (1.0)	0	7 (1.4)	5 (1.0)
<b>Vascular Disorders</b>				
Hemorrhage	163 (33.3)	10 (2.0)	81 (16.6)	4 (0.8)
Hypertension	26 (5.3)	6 (1.2)	11 (2.3)	2 (0.4)

**Table 6 Summary of Selected Adverse Events\* (AEs) Occurring with an Overall ≥2% Higher Incidence in Patients within the Kadcyla Treatment Arm Compared to the Lapatinib + Capecitabine Treatment Arm in the Randomized Study TDM4370g/BO21977 (EMILIA)**

Selected Adverse Event Category MedDRA Preferred Term	Kadcyla (3.6 mg/kg) n=490 Frequency %	Lapatinib (1250 mg) + Capecitabine (2000 mg/m <sup>2</sup> ) n=488 Frequency %
	All grades n (%)	All grades n (%)
<b>Eye Disorders</b>		
-Overall-	36 (7.3)	11 (2.3)
Vision Blurred	22 (4.5)	4 (0.8)
Visual Impairment	7 (1.4)	2 (0.4)
Visual Acuity Reduced	4 (0.8)	3 (0.6)
Photopsia	2 (0.4)	0
Amblyopia	1 (0.2)	0
Blindness Transient	1 (0.2)	0
Diplopia	0	1 (0.2)
Optic Neuropathy	1 (0.2)	0
Scintillating Scotoma	0	1 (0.2)
<b>Hemorrhage</b>		
-Overall-	163 (33.3)	81 (16.6)
Epistaxis	113 (23.1)	41 (8.4)
Gingival Bleeding	21 (4.3)	7 (1.4)
Vaginal Hemorrhage	13 (2.7)	9 (1.8)

<b>Selected Adverse Event Category MedDRA Preferred Term</b>	<b>Kadcyla (3.6 mg/kg) n=490 Frequency %</b>	<b>Lapatinib (1250 mg) + Capecitabine (2000 mg/m<sup>2</sup>) n=488 Frequency %</b>
	<b>All grades n (%)</b>	<b>All grades n (%)</b>
Contusion	8 (1.6)	5 (1.0)
Rectal Hemorrhage	8 (1.6)	5 (1.0)
Petechiae	12 (2.4)	0
Hematochezia	6 (1.2)	4 (0.8)
Menorrhagia	3 (0.6)	4 (0.8)
Metrorrhagia	5 (1.0)	2 (0.4)
Hematoma	6 (1.2)	0
Hemoptysis	4 (0.8)	2 (0.4)
Ecchymosis	5 (1.0)	0
Hemorrhoidal Hemorrhage	1 (0.2)	3 (0.6)
Skin Hemorrhage	2 (0.4)	2 (0.4)
Gastrointestinal Hemorrhage	2 (0.4)	0
Hemorrhage	1 (0.2)	1 (0.2)
Lip Hemorrhage	1 (0.2)	1 (0.2)
Mouth Hemorrhage	2 (0.4)	0
Tongue Hemorrhage	2 (0.4)	0
Anal Hemorrhage	0	1 (0.2)
Conjunctival Hemorrhage	1 (0.2)	0
Cystitis Hemorrhage	0	1 (0.2)
Extradural Hematoma	0	1 (0.2)
Genital Hemorrhage	0	1 (0.2)
Hematemesis	0	1 (0.2)
Hematuria	0	1 (0.2)
Hemorrhagic Diathesis	1 (0.2)	0
Intestinal Hemorrhage	1 (0.2)	0
Nail Bed Bleeding	0	1 (0.2)
Nipple Exudate Bloody	0	1 (0.2)
Pelvic Hematoma	1 (0.2)	0
Peptic Ulcer Hemorrhage	0	1 (0.2)
Post Procedural Hematoma	1 (0.2)	0
Post Procedural Hemorrhage	1 (0.2)	0
Purpura	0	1 (0.2)
Subdural Hemorrhage	0	1 (0.2)
Tumour Hemorrhage	0	1 (0.2)
Ulcer Hemorrhage	1 (0.2)	0
Upper Gastrointestinal Hemorrhage	1 (0.2)	0
Uterine Hemorrhage	1 (0.2)	0
Wound Hemorrhage	0	1 (0.2)
<b>Hepatotoxicity</b>		
-Overall-	159 (32.4)	128 (26.2)
Aspartate Aminotransferase Increased	113 (23.1)	49 (10.0)
Alanine Aminotransferase Increased	87 (17.8)	45 (9.2)

<b>Selected Adverse Event Category MedDRA Preferred Term</b>	<b>Kadcyla (3.6 mg/kg) n=490 Frequency %</b>	<b>Lapatinib (1250 mg) + Capecitabine (2000 mg/m<sup>2</sup>) n=488 Frequency %</b>
	<b>All grades n (%)</b>	<b>All grades n (%)</b>
Hyperbilirubinemia	8 (1.6)	44 (9.0)
Blood Bilirubin Increased	15 (3.1)	31 (6.4)
Blood Alkaline Phosphatase Increased	23 (4.7)	18 (3.7)
Transaminases Increased	16 (3.3)	5 (1.0)
Gamma-Glutamyltransferase Increased	10 (2.0)	0
Hypoalbuminemia	4 (0.8)	4 (0.8)
Liver Function Test Abnormal	4 (0.8)	3 (0.6)
Cytolytic Hepatitis	3 (0.6)	3 (0.6)
Jaundice	0	4 (0.8)
Hepatic Enzyme Increased	2 (0.4)	1 (0.2)
Hepatic Pain	3 (0.6)	0
Portal Hypertension	2 (0.4)	0
Spider Naevus	2 (0.4)	0
Aspartate Aminotransferase Abnormal	1 (0.2)	0
Hepatic Function Abnormal	0	1 (0.2)
Hepatitis Toxic	1 (0.2)	0
Hepatotoxicity	1 (0.2)	0
Hypertransaminasemia	0	1 (0.2)
<b>IRR Hypersensitivity</b>		
-Overall-	21 (4.3)	0
Hypersensitivity	7 (1.4)	0
Infusion Related Reaction	7 (1.4)	0
Face Edema	3 (0.6)	0
Urticaria	2 (0.4)	0
Eye Edema	1 (0.2)	0
Pharyngeal Edema	1 (0.2)	0
<b>Peripheral Neuropathy</b>		
-Overall-	127 (25.9)	92 (18.9)
Neuropathy Peripheral	53 (10.8)	28 (5.7)
Peripheral Sensory Neuropathy	32 (6.5)	26 (5.3)
Paraesthesia	31 (6.3)	18 (3.7)
Hypoaesthesia	14 (2.9)	9 (1.8)
Muscular Weakness	6 (1.2)	11 (2.3)
Neurotoxicity	6 (1.2)	2 (0.4)
Peripheral Motor Neuropathy	5 (1.0)	2 (0.4)
Burning Sensation	3 (0.6)	2 (0.4)
Polyneuropathy	4 (0.8)	1 (0.2)
Gait Disturbance	1 (0.2)	3 (0.6)
Neuralgia	3 (0.6)	1 (0.2)
Sensory Disturbance	1 (0.2)	3 (0.6)
Dyaesthesia	1 (0.2)	1 (0.2)

<b>Selected Adverse Event Category MedDRA Preferred Term</b>	<b>Kadcyla (3.6 mg/kg) n=490 Frequency %</b>	<b>Lapatinib (1250 mg) + Capecitabine (2000 mg/m<sup>2</sup>) n=488 Frequency %</b>
	<b>All grades n (%)</b>	<b>All grades n (%)</b>
Formication	2 (0.4)	0
Motor Dysfunction	1 (0.2)	1 (0.2)
Areflexia	1 (0.2)	0
Hypotonia	0	1 (0.2)
Skin Burning sensation	0	1 (0.2)
<b>Thrombocytopenia</b>		
-Overall-	155 (31.6)	16 (3.3)
Thrombocytopenia	143 (29.2)	14 (2.9)
Platelet Count Decreased	14 (2.9)	3 (0.6)
Platelet Disorder	1 (0.2)	0

\*Adverse Event – defined as an event reported regardless of causality

**Table 7 Summary of ADRs occurring in ≥1% of MBC patients treated with Kadcyla**

<b>ADR (MedDRA) System Organ Class</b>	<b>Kadcyla</b>	
	<b>All grades n (%) n = 884</b>	<b>Grade 3 – 5 n (%) n = 884</b>
<b>Blood and Lymphatic System Disorders</b>		
Thrombocytopenia	284 (32.1)	105 (11.9)
Anemia	153 (17.3)	31 (3.5)
Neutropenia	68 (7.7)	19 (2.1)
Leukopenia	46 (5.2)	5 (0.6)
<b>Cardiac Disorders</b>		
Left ventricular dysfunction	19 (2.1)	3 (0.3)
<b>Eye Disorders</b>		
Dry eye	51 (5.8)	0
Lacrimation increased	42 (4.8)	0
Vision blurred	45 (5.1)	0
Conjunctivitis	37 (4.2)	0
<b>Gastrointestinal Disorders</b>		
Nausea	380 (43.0)	10 (1.1)
Constipation	234 (26.5)	5 (0.6)
Vomiting	185 (20.9)	8 (0.9)
Diarrhea	188 (21.3)	9 (1.0)
Dry Mouth	165 (18.7)	0
Abdominal pain	166 (18.8)	8 (0.9)
Stomatitis	133 (15.0)	1 (0.1)
Dyspepsia	82 (9.3)	1 (0.1)
Gingival bleeding	31 (3.5)	0
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	410 (46.4)	28 (3.2)
Pyrexia	209 (23.6)	3 (0.3)
Asthenia	125 (14.1)	8 (0.9)
Chills	95 (10.7)	0
Edema peripheral	81 (9.2)	1 (0.1)

ADR (MedDRA)	Kadcyla	
	All grades n (%) n = 884	Grade 3 – 5 n (%) n = 884
<b>System Organ Class</b>		
<b>Immune System Disorders</b>		
Drug hypersensitivity	25 (2.8)	0
<b>Infections and Infestations</b>		
Urinary tract infection	122 (13.8)	3 (0.3)
<b>Injury, Poisoning, and Procedural Complications</b>		
Infusion related reaction	40 (4.5)	1 (0.1)
<b>Investigations</b>		
Transaminases increased	253 (28.6)	64 (7.2)
Blood alkaline phosphatase increased	57 (6.4)	4 (0.5)
<b>Metabolism and Nutrition Disorders</b>		
Hypokalemia	142 (16.1)	29 (3.3)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal pain	361 (40.8)	28 (3.2)
Arthralgia	178 (20.1)	8 (0.9)
Myalgia	110 (12.4)	3 (0.3)
<b>Nervous System Disorders</b>		
Headache	260 (29.4)	5 (0.6)
Peripheral neuropathy	199 (22.5)	15 (1.7)
Dizziness	88 (10.0)	3 (0.3)
Dysgeusia	70 (7.9)	0
Memory impairment	12 (1.4)	1 (0.1)
<b>Psychiatric Disorders</b>		
Insomnia	105 (11.9)	2 (0.2)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Epistaxis	223 (25.2)	4 (0.5)
Cough	181 (20.5)	1 (0.1)
Dyspnea	131 (14.8)	13 (1.5)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	115 (13.0)	0
Pruritus	49 (5.5)	1 (0.1)
Alopecia	33 (3.7)	0
Nail disorder	26 (2.9)	0
Palmar–plantar erythrodysesthesia syndrome	11 (1.2)	0
Urticaria	10 (1.1)	0
<b>Vascular Disorders</b>		
Hemorrhage	323 (36.5)	18 (2.0)
Hypertension	58 (6.6)	9 (1.0)

### **Early Breast Cancer**

The safety of Kadcyla has been evaluated in 740 patients with EBC in Study BO27938 (KATHERINE) treated in the adjuvant setting with up to 14 cycles of Kadcyla. The patients enrolled on study had residual invasive disease following neoadjuvant trastuzumab and taxane-based therapy.

Table 8 summarizes the ADRs that have been reported in association with the use of Kadcyla in the pivotal study BO27938 (KATHERINE).

**Table 8 Summary of ADRs Occurring in ≥ 1% of Patients on the Kadcyła Treatment Arm in the Randomized Study BO27938 (KATHERINE)**

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=740 Frequency %		Trastuzumab (6 mg/kg) n=720 Frequency%	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
<b>Blood and Lymphatic System Disorders</b>				
Thrombocytopenia	211 (28.5)	42 (5.7)	17 (2.4)	2 (0.3)
Anemia	75 (10.1)	8 (1.1)	62 (8.6)	1 (0.1)
Neutropenia	61 (8.2)	9 (1.2)	36 (5.0)	5 (0.7)
Leukopenia	61 (8.2)	0	42 (5.8)	1 (0.1)
<b>Cardiac Disorders</b>				
Left ventricular dysfunction	22 (3.0)	4 (0.5)	35 (4.9)	7 (1.0)
<b>Eye Disorders</b>				
Lacrimation increased	41 (5.5)	0	13 (1.8)	0
Dry eye	33 (4.5)	0	16 (2.2)	0
Vision Blurred	29 (3.9)	0	17 (2.4)	0
Conjunctivitis	26 (3.5)	0	14 (1.9)	0
<b>Gastrointestinal Disorders</b>				
Nausea	308 (41.6)	4 (0.5)	94 (13.1)	2 (0.3)
Diarrhea	91 (12.3)	6 (0.8)	90 (12.5)	2 (0.3)
Constipation	126 (17.0)	1 (0.1)	59 (8.2)	0
Stomatitis	112 (15.1)	1 (0.1)	57 (7.9)	1 (0.1)
Vomiting	108 (14.6)	4 (0.5)	37 (5.1)	2 (0.3)
Abdominal pain	79 (10.7)	3 (0.4)	49 (6.8)	2 (0.3)
Dry Mouth	100 (13.5)	1 (0.1)	9 (1.3)	0
Dyspepsia	32 (4.3)	0	26 (3.6)	0
Gingival bleeding	9 (1.2)	0	1 (0.1)	0
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	366 (49.5)	8 (1.1)	243(33.8)	1 (0.1)
Pyrexia	77 (10.4)	0	29 (4.0)	0
Peripheral edema	29 (3.9)	0	52 (7.2)	0
Chills	39 (5.3)	0	14 (1.9)	0
<b>Immune System Disorders</b>				
Drug hypersensitivity	20 (2.7)	3 (0.4)	15 (2.1)	1 (0.1)
<b>Infections and Infestations</b>				
Urinary tract infection	77 (10.4)	2 (0.3)	44 (6.1)	1 (0.1)
<b>Injury, Poisoning, and Procedural Complications</b>				
Radiation Pneumonitis	11 (1.5)	2 (0.3)	5 (0.7)	0
Infusion-related reaction	12 (1.6)	0	4 (0.6)	0
<b>Investigations</b>				
Increased transaminases	240 (32.4)	11 (1.5)	57 (7.9)	3 (0.4)
Blood alkaline phosphatase increased	61 (8.2)	1 (0.1)	13 (1.8)	0

Adverse Drug Reactions (MedDRA) System Organ Class	Kadcyla (3.6 mg/kg) n=740 Frequency %		Trastuzumab (6 mg/kg) n=720 Frequency%	
	All grades n (%)	Grade 3 – 4 n (%)	All grades n (%)	Grade 3 – 4 n (%)
Blood Bilirubin Increased	49 (6.6)	0	2 (0.3)	0
<b>Metabolism and Nutrition Disorders</b>				
Hypokalemia	50 (6.8)	9 (1.2)	14 (1.9)	1 (0.1)
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal pain	225 (30.4)	5 (0.7)	209 (29.0)	5 (0.7)
Arthralgia	192 (25.9)	1 (0.1)	148 (20.6)	0
Myalgia	114 (15.4)	0	80 (11.1)	0
<b>Nervous System Disorders</b>				
Headache	210 (28.4)	0	122 (16.9)	1 (0.1)
Peripheral neuropathy	207 (28.0)	12 (1.6)	102 (14.2)	1 (0.1)
Dizziness	70 (9.5)	1 (0.1)	57 (7.9)	2 (0.3)
Dysgeusia	60 (8.1)	0	11 (1.5)	0
<b>Psychiatric Disorders</b>				
Insomnia	101 (13.6)	0	86 (11.9)	1 (0.1)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Cough	100 (13.5)	1 (0.1)	86 (11.9)	0
Epistaxis	159 (21.5)	0	25 (3.5)	0
Dyspnea	62 (8.4)	1 (0.1)	53 (7.4)	0
Pneumonitis	8 (1.1)	1 (0.1)	1 (0.1)	0
<b>Skin and Subcutaneous Tissue Disorders</b>				
Pruritus	51 (6.9)	0	42 (5.8)	1 (0.1)
Alopecia	18 (2.4)	0	7 (1.0)	0
Urticaria	9 (1.2)	0	6 (0.8)	1 (0.1)
Rash	8 (1.1)	0	7 (1.0)	0
Palmar-plantar erythrodysesthesia syndrome	8 (1.1)	0	6 (0.8)	0
<b>Vascular Disorders</b>				
Hemorrhage	216 (29.2)	2 (0.3)	69 (9.6)	2 (0.3)
Hypertension	42 (5.7)	15 (2.0)	35 (4.9)	9 (1.3)

### 8.3 Less Common Clinical Trial Adverse Reactions

The following significant adverse reactions were reported at an incidence of < 1%:

#### Metastatic Breast Cancer

**Hepatobiliary Disorders:** Hepatic Failure (0.1%), Hepatotoxicity (0.3%), Nodular Regenerative Hyperplasia (0.1%), Portal Hypertension (0.1%)

**Respiratory, Thoracic, and Mediastinal Disorders:** Pneumonitis (0.9%)

#### Early Breast Cancer

**Nervous System Disorders:** Memory Impairment (0.9%)

**General Disorders and Administration:** Asthenia (0.4%)

**Skin and Subcutaneous Tissue Disorder:** Nail Disorder (0.3%)

**Hepatobiliary Disorders:** Nodular Regenerative Hyperplasia (0.3%)

## 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

### Metastatic Breast Cancer

The following table displays laboratory abnormalities observed in patients treated with Kadcyła in clinical trial TDM4370g/BO21977 (EMILIA).

**Table 9 Laboratory abnormalities observed in patients in study TDM4370g/BO21977 (EMILIA)**

Parameter	Kadcyła (3.6 mg/kg)			Lapatinib (1250 mg) + Capecitabine (2000 mg/m <sup>2</sup> )		
	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Hematologic</b>						
Decreased platelet count	407 (84)	69 (14)	15 (3)	101 (21)	2 (<1)	3 (<1)
Decreased hemoglobin	300 (62)	20 (4)	5 (1)	312 (64)	14 (3)	1 (<1)
Decreased neutrophils	186 (39)	17 (4)	3 (<1)	184 (38)	30 (6)	10 (2)
<b>Hepatic</b>						
Increased bilirubin	95 (20)	3 (<1)	0 (0)	276 (57)	11 (2)	0 (0)
Increased AST	475 (98)	35 (7)	2 (<1)	311 (65)	12 (3)	0 (0)
Increased ALT	397 (82)	23 (5)	1 (<1)	259 (54)	14 (3)	0 (0)
<b>Potassium</b>						
Decreased potassium	148 (34)	14 (3)	1 (<1)	132 (31)	26 (6)	4 (<1)

### Early Breast Cancer

The following table displays laboratory abnormalities observed in patients treated with Kadcyła in clinical trial BO27938 (KATHERINE).

**Table 10 Laboratory abnormalities observed in patients in Study BO27938 (KATHERINE)**

Parameter	Kadcyła			Trastuzumab		
	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Hepatic</b>						
Increased Bilirubin	85 (12)	0	0	26 (4)	2 (<1)	3 (<1)
Increased AST	583 (79)	6 (<1)	0	153 (21)	14 (3)	1 (<1)
Increased ALT	409 (55)	409 (<1)	0	150 (21)	30 (6)	10 (2)
<b>Hematologic</b>						
Decreased Platelets	347 (51)	29 (4)	16 (2)	92 (13)	11 (2)	0 (0)
Decreased Hemoglobin	229 (31)	8 (1)	0	206 (29)	12 (3)	0 (0)
Decreased Neutrophils	174 (24)	10 (1)	0	133 (19)	14 (3)	0 (0)
<b>Potassium</b>						
Decreased Potassium	191 (26)	15 (2)	4 (<1)	68 (9)	26 (6)	4 (<1)

## **Additional Information on Selected Adverse Reactions**

### **Death**

In the metastatic setting, five deaths (1%) due to reasons other than progressive disease occurred in each arm of the pivotal trial. In the Kadcyła arm, four of the five patients had neutropenic sepsis/infection, pneumonia or metabolic encephalopathy, and died between 21-35 days after the last dose of Kadcyła. In the lapatinib and capecitabine arm, the five deaths were due to coronary artery disease, multi-organ failure, coma, hydrocephalus or acute respiratory distress syndrome. In the other Kadcyła MBC clinical trials, two patients treated with Kadcyła died of an unknown cause while nine additional patients had AEs leading to death. These patients had hepatic failure, abnormal hepatic function, bacterial sepsis, respiratory failure, interstitial lung disease or sudden death. Fatal cases of hepatic failure, abnormal hepatic function and metabolic encephalopathy are also described in the 7 WARNINGS and PRECAUTIONS: Hepatotoxicity

In the EBC setting, one fatal AE (intracranial hemorrhage) occurred with Kadcyła. There were 5 deaths which occurred more than 30 days after the last study treatment and were not related to study treatment or study procedures due to reasons other than progressive disease. In the Kadcyła arm, one death was due to cerebrovascular event with renal insufficiency and another reported as death after osteosynthesis. In the trastuzumab arm, two deaths were due to pneumonia and one due to a cerebrovascular event.

### **Immunogenicity**

As with all therapeutic proteins, there is the potential for an immune response to Kadcyła. A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to Kadcyła. Following Kadcyła dosing, 5.1% (63/1243) of patients tested positive for anti-Kadcyła antibodies at one or more post-dose time points. In the Phase I and Phase II studies, 6.4% (24/376) of patients tested positive for anti-Kadcyła antibodies. In the EMILIA study (TDM4370g/BO21977), 5.2% (24/466) of patients tested positive for anti-Kadcyła antibodies, of which 13 patients also tested positive for neutralizing antibodies. In the KATHERINE (BO27938) study, 3.7% (15/401) of patients tested positive for anti-Kadcyła antibodies, of which 5 patients also tested positive for neutralizing antibodies. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti-Kadcyła antibodies on the pharmacokinetics, safety, and efficacy of Kadcyła.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Kadcyła with the incidence of antibodies to other products may be misleading.

## **8.5 Post-Market Adverse Reactions**

No new ADRs have been identified in the post-market setting.

## **9 DRUG INTERACTIONS**

### **9.2 Drug Interactions Overview**

Interactions with Kadcyła have not been established.

## 9.4 Drug-Drug Interactions

No formal drug-drug interaction studies with Kadcyła (trastuzumab emtansine) in humans have been conducted. *In vitro* metabolism studies in human liver microsomes suggest that DM1, the cytotoxic component of Kadcyła (trastuzumab emtansine), is metabolized mainly by CYP3A4 and, to a lesser extent, by CYP3A5. DM1 does not induce or inhibit P450-mediated metabolism *in vitro*. Caution should be taken when Kadcyła is co-administered with potent CYP3A inhibitors.

Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with Kadcyła should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying Kadcyła treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and Kadcyła treatment cannot be delayed, patients should be closely monitored for adverse reactions.

## 9.5 Drug-Food Interactions

Interactions with food have not been established.

## 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

## 9.7 Drug-Laboratory Test Interactions

No drug-laboratory interactions have been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Kadcyła, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab. Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Kadcyła has the mechanisms of action of both trastuzumab and DM1

- Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, Kadcyła, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signaling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.

- DM1, the cytotoxic drug component of Kadcyła, binds to tubulin. By inhibiting tubulin polymerization, DM1 causes cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from *in vitro* cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.
- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

## 10.2 Pharmacodynamics

The anti-tumor activity of trastuzumab emtansine was evaluated in HER2-overexpressing human breast cancer cells *in vitro* and in mouse tumor xenograft models. In trastuzumab-sensitive cancer cells, trastuzumab emtansine is more potent than trastuzumab both *in vitro* and *in vivo*. Moreover, both trastuzumab-insensitive and lapatinib-resistant breast cancer cells are highly sensitive to trastuzumab emtansine. In preclinical studies, trastuzumab emtansine was demonstrated to retain therapeutic properties of trastuzumab such as inhibition of HER2 extracellular domain shedding, suppression of HER2-activated signaling pathways, and mediation of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, the direct effect of trastuzumab is cytostasis due to arrest of cells in the G1 cell cycle phase, with no induction of cell death. As expected of an anti-mitotic agent, treatment with trastuzumab emtansine results in mitotic (G2/M phase) arrest, apoptosis (programmed cell death) and cellular lysis in HER2-overexpressing breast cancer cells.

## 10.3 Pharmacokinetics

The population pharmacokinetic analysis of trastuzumab emtansine suggested no difference in Kadcyła exposure based on disease status (adjuvant vs. metastatic setting).

**Absorption:** Kadcyła is administered intravenously. There have been no studies performed with other routes of administration.

**Distribution:** In the phase I study TDM3569g and the phase III study BO27938, Kadcyła when administered intravenously every 3 weeks exhibited linear pharmacokinetics (i.e., linear increase of  $C_{max}$  and  $AUC_{inf}$ ) across doses ranging from 2.4 to 4.8 mg/kg; patients who received doses less than or equal to 1.2 mg/kg had faster clearance. Patients in Study TDM4370g/BO21977 and Study BO27938 who received 3.6 mg/kg of Kadcyła intravenously every 3 weeks had a mean ( $\pm$ SD) maximum serum concentration ( $C_{max}$ ) of trastuzumab emtansine in Cycle 1 of 83.4 ( $\pm$ 16.5)  $\mu$ g/mL (n=292) and 72.6 ( $\pm$  24.3)  $\mu$ g/mL, respectively. The mean steady-state volume of distribution ( $V_{ss}$ ) in patients who received 3.6 mg/kg of Kadcyła every 3 weeks ranged from 28.4 to 58.4 mL/kg across six Phase I/II/III clinical studies.

**Metabolism:** Kadcyła is expected to undergo catabolism by means of proteolysis in cellular lysosomes, with no significant involvement of cytochrome P450 isoenzymes. Catabolites including Lys-MCC-DM1, MCC-DM1 and DM1 are detected at low levels in human plasma. In Study TDM4370g/BO21977 and Study BO27938, mean ( $\pm$ SD) maximum DM1 levels in Cycle 1 following Kadcyła administration were consistently low and averaged 4.61 ( $\pm$  1.61) ng/mL (n=287) and 4.71 ( $\pm$  2.25) ng/mL, respectively.

*In vitro* metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5.

**Excretion:** The pharmacokinetics of Kadcyła when administered intravenously at 3.6 mg/kg every three weeks were similar in HER2-positive metastatic breast cancer patients across the six clinical studies. The mean clearance ranged from 7 to 13 mL/day/kg and the estimated mean terminal half-life ranged from 3.1 to 4.5 days across the six studies. No accumulation of trastuzumab emtansine was observed after repeated dosing of IV infusion every 3 weeks.

The body weight based dose of 3.6 mg/kg every 3 weeks is considered appropriate based on efficacy and safety data observed in the clinical studies.

In nonclinical studies, catabolites of trastuzumab emtansine including DM1, Lys-MCC-DM1, and MCC-DM1 are mainly excreted in the bile with minimal elimination in urine.

### Special Populations and Conditions

**Geriatrics (≥65 years of age):** Analysis of the key PK parameters of trastuzumab emtansine (i.e., CL, V<sub>ss</sub>, AUC<sub>inf</sub>, and C<sub>max</sub>) for patients who received 3.6 mg/kg every 3 weeks across the six studies showed that age (<65 (n=532); 65-75 (n= 72); >75 (n=17)) did not have a clinical meaningful effect on the pharmacokinetics of Kadcyła.

**Sex:** Because most of the patients in Kadcyła clinical studies were females, effect of gender on the pharmacokinetics of Kadcyła was not formally evaluated.

**Ethnic origin:** Ethnic origin did not appear to influence the pharmacokinetics of Kadcyła. The key PK parameters of Kadcyła (i.e., CL, V<sub>ss</sub>, AUC<sub>inf</sub>, and C<sub>max</sub>) when administered at 3.6 mg/kg every 3 weeks in White patients (n=489) were comparable to those in Asian patients (n=70).

**Hepatic Insufficiency:** The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of Kadcyła to metastatic HER2-positive breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment.

- Plasma concentrations of DM1 and DM1-containing catabolites (Lys-MCC-DM1 and MCC-DM1) were low and variable between patients with and without hepatic impairment. AUC for DM1 and DM1-containing catabolites has not been determined as most of the measured concentrations are below assay quantitation limits.
- Systemic exposures (AUC) of trastuzumab emtansine at Cycle 1 in patients with mild and moderate hepatic impairment were approximately 38% and 67% lower than that of patients with normal hepatic function, respectively. Trastuzumab emtansine exposure (AUC) at Cycle 3 after repeated dosing in patients with mild hepatic dysfunction was 14% lower compared to patients with normal hepatic function. There are insufficient data to characterize trastuzumab emtansine exposure beyond Cycle 1 in patients with moderate hepatic impairment.

No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe hepatic impairment (Child-Pugh class C).

**Renal Insufficiency:** The key PK parameters of trastuzumab emtansine (i.e., CL, V<sub>ss</sub>, AUC<sub>inf</sub>, and C<sub>max</sub>) when administered at 3.6 mg/kg every 3 weeks in patients with mild (creatinine clearance CL<sub>cr</sub> 60-89 mL/min, n=237) and moderate (CL<sub>cr</sub> 30 to 59 mL/min, n=45) renal impairment were similar to those in patients with normal renal function (CL<sub>cr</sub> ≥90 mL/min, n=337). Pharmacokinetic data in patients with severe renal impairment (CL<sub>cr</sub> 15-29 mL/min) is limited (n=1), therefore no dosage recommendations can be made.

## 11 STORAGE, STABILITY AND DISPOSAL

### Storage of Vials:

Store unreconstituted vials at 2–8°C.

This medicine should not be used after the expiry date (EXP) shown on the pack.

### Shelf-life of the reconstituted solution:

Product vials reconstituted with sterile water for injection should be used immediately following reconstitution. If not used immediately, the reconstituted vials can be stored for up to 24 hours at 2-8°C, and must be discarded thereafter.

Do not freeze the reconstituted solution.

### Shelf-life of the solution for infusion containing the reconstituted product:

The reconstituted Kadcyła solution diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin bags containing 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection, may be stored at 2–8°C for up to 24 hours prior to use. This storage time is in addition to the time allowed for the reconstituted vials. Particulates may be observed on storage if diluted in 0.9% Sodium Chloride Injection, therefore, a 0.2-micron in-line (non-protein adsorptive) /0.22 micron polyethersulfone (PES) filter is required for administration (see 4 DOSAGE AND ADMINISTRATION).

Do not freeze the solution for infusion containing the reconstituted product.

## 12 SPECIAL HANDLING INSTRUCTIONS

### Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Local requirements should be followed for the disposal process of unused/expired medicines or waste material.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

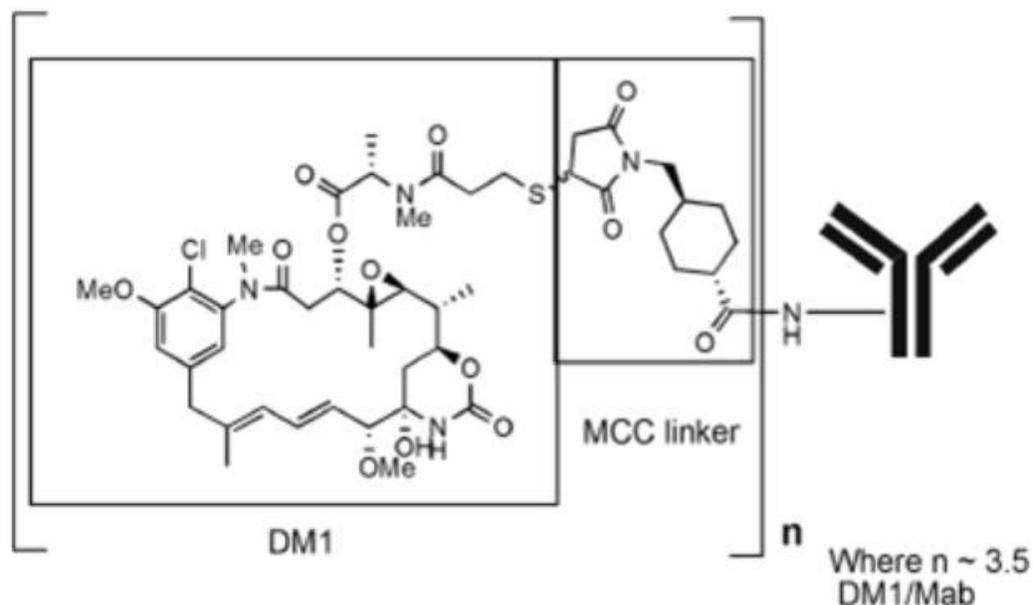
#### Drug Substance

Proper name: trastuzumab emtansine

Chemical name: Immunoglobulin G1, anti-(human p185neu receptor) (human-mouse monoclonal rhuMab HER2  $\gamma$ 1-chain), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer, tetraamide with  $N^2$ -[3-[[1-(4-carboxycyclohexyl) methyl]-2,5-dioxo-3-pyrrolidinyl]thio]-1-oxopropyl]- $N^2$ '-deacetylmaytansine

Molecular mass: 148,781 Da

Structural formula:



#### Product Characteristics:

Kadcyla (trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule-inhibitory drug DM1 (a derivative of maytansine) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.

### 14 CLINICAL TRIALS

#### 14.1 Clinical Trials by Indication

##### Metastatic Breast Cancer (MBC)

An overview of the study designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 11.

**Table 11 Summary of trial design and patient demographics for clinical trials in Metastatic Breast Cancer (MBC)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TDM4370g / BO21977 (EMILIA)	A Phase III randomized, multicenter, open-label study	Kadcyla: 3.6 mg/kg q3w, IV or Lapatinib 1250 mg/day, po + Capecitabine 1000 mg/m <sup>2</sup> twice daily on Days 1-14	Kadcyla: 495 patients treated  Lapatinib + Capecitabine : 496 patients treated	Kadcyla: 52.2 (25 - 84)  Lapatinib + Capecitabine: 53.2 (24 - 83)	Kadcyla: Female: 494 (99.8%) Male: 1 (0.2%)  Lapatinib + Capecitabine: Female: 492 (99.2%) Male: 4 (0.8%)
TDM4450g/ BO21976	A Phase II randomized, multicenter, open-label, study	Kadcyla: 3.6 mg/kg q3w, IV or Trastuzumab: 8 mg/kg loading dose; 6mg/kg q3w, IV + Docetaxel: 75 or 100 mg/m <sup>2</sup> q3w, IV	Kadcyla: 67 patients treated  Trastuzumab + Docetaxel: 70 patients enrolled, (2 not treated)	Kadcyla: 54.3 (27 - 82)  Trastuzumab + Docetaxel: 52.1 (33-75)	Kadcyla: Female: 67 (100.0%)  Trastuzumab + Docetaxel: Female: 70 (100.0%)
TDM4374g	A Phase II, single-arm, open-label study	Kadcyla: 3.6 mg/kg q3w , IV	110 patients treated	53.0 (34 - 77)	Female: 108 (98.2%) Male: 2 (1.8%)
TDM4258g	A Phase II single-arm, open-label study	Kadcyla: 3.6 mg/kg q3w, IV	112 treated patients	55.0 (33 - 82)	Female: 111 (99.1%) Male: 1 (0.9%)

**Study Results in Metastatic Breast Cancer (MBC)**

A Phase III, randomized, multicentre, international, open-label clinical trial (TDM4370g/BO21977) was conducted in patients with HER2-positive unresectable locally advanced breast cancer (LABC) or MBC who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed within six months of completing adjuvant therapy. Prior to enrollment, breast tumour samples were required to be centrally confirmed for HER2-positive disease defined as a score of 3+ by IHC or gene amplification by ISH. The study compared the safety and efficacy of Kadcyla with that of lapatinib plus capecitabine. A total of 991 patients were randomized (1:1) to Kadcyla or lapatinib plus capecitabine as follows:

- Kadcyła Arm (n=495): Kadcyła 3.6 mg/kg intravenously (IV) over 30–90 minutes on Day 1 of a 21-day cycle
- Control Arm (lapatinib plus capecitabine) (n=496): lapatinib 1250 mg/day orally once per day of a 21-day cycle plus capecitabine 1000 mg/m<sup>2</sup> orally twice daily on Days 1–14 of a 21-day cycle

Patients received Kadcyła or lapatinib plus capecitabine until progression of disease (as assessed by the investigator), withdrawal of consent or unmanageable toxicity. At the time of the primary analysis, median time on study drug was 5.7 months (range: 0-28.4) for Kadcyła, 4.9 months (range: 0-30.8) for lapatinib, and 4.8 months (range: 0-30.4) for capecitabine. At the time of the second interim analysis, the median time on study drug was 7.6 months (range 0-34.8) for Kadcyła, 5.5 months (range 0-33.3) for lapatinib, and 5.3 months (range 0-33.3) for capecitabine. Randomization was stratified by world region (United States, Western Europe, other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0-1, >1) and visceral versus non-visceral disease as determined by the investigators.

Baseline patient and tumour characteristics were well balanced between treatment groups. All patients had metastatic disease at study entry. Patient demographics are summarized in Table 12.

**Table 12 Patient Demographics TDM4370g/BO21977 (EMILIA) study**

	<b>Lapatinib+Capecitabine N = 496</b>	<b>Kadcyła N = 495</b>
<b>Age (years)</b>		
Median	53	53
Range	24-83	25-84
<b>Sex, n (%)</b>		
Female	492 (99.2)	494 (99.8)
Male	4 (0.8)	1 (0.2)
<b>Race, n (%)</b>		
Caucasian	374 (75.4)	358 (72.3)
Asian	86 (17.3)	94 (19.0)
Black	21 (4.2)	29 (5.9)
Other	10 (2)	7 (1.4)
Not available	5 (1.0)	7 (1.4)
<b>ECOG Performance status, n (%)</b>		
0	312 (62.9)	299 (60.4)
1	176 (35.5)	194 (39.2)
Not available	8 (1.6)	2 (<1)
<b>Site of disease involvement, n (%)</b>		
Visceral	335 (67.5)	334 (67.5)
Nonvisceral	161 (32.5)	161 (32.5)
<b>Hormone-receptor status, n (%)</b>		
ER-positive, PR-positive, or both	263 (53)	282 (57.0)
ER-negative and PR-negative	224 (45.2)	202 (40.8)
Unknown, ER-negative PR unknown	9 (1.8)	11 (2.3)
<b>Number of metastatic sites (IRC)</b>		
1	151 (30.4)	143 (28.9)
2	156 (31.5)	155 (31.3)
3+	175 (35.3)	189 (38.2)

	<b>Lapatinib+Capecitabine N = 496</b>	<b>Kadcyla N = 495</b>
Missing	14 (2.8)	8 (1.6)
<b>Measurable disease (IRC)</b>		
No	107 (21.6)	98 (19.8)
Yes	389 (78.4)	397 (80.2)
<b>Prior chemotherapy regimens for locally advanced or metastatic disease</b>		
0-1	305 (61.5)	304 (61.4)
>1	191 (38.5)	191 (38.6)

The majority of patients (88%) had received prior systemic treatment in the metastatic setting. Twelve percent of patients had prior treatment only in the neoadjuvant or adjuvant setting and had disease relapse within 6 months of treatment. All but one patient received trastuzumab prior to study entry; approximately 85% of patients received prior trastuzumab in the metastatic setting. Over 99% percent of patients had received a taxane, and 61% of patients had received an anthracycline prior to study entry. Overall, patients received a median of 3 systemic agents in the metastatic setting. Among patients with hormone receptor-positive tumours, 44.4% received prior adjuvant hormonal therapy and 44.8% received hormonal therapy for locally advanced/metastatic disease.

The co-primary efficacy endpoints of the study were progression-free survival (PFS) as assessed by an independent review committee (IRC), and overall survival (OS). PFS was defined as the time from randomization to documented IRC-assessed PD or death from any cause (whichever occurred earlier). OS was defined as the time from the date of randomization to the date of death from any cause.

Key secondary endpoints included PFS (investigator-assessed), the objective response rate (ORR), the duration of response, and the time to symptom progression.

**Table 13 Summary of efficacy from TDM4370g/BO21977 (EMILIA) study**

	<b>Lapatinib+Capecitabine N = 496</b>	<b>Kadcyla N = 495</b>
<b>Primary Endpoints</b>		
<b>IRC-assessed PFS</b>		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549 , 0.771)	
p-value (Log-Rank test, stratified*)	<0.0001	
<b>Overall Survival**</b>		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard Ratio (stratified*)	0.682	

	<b>Lapatinib+Capecitabine</b> <b>N = 496</b>	<b>Kadcyla</b> <b>N = 495</b>
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test*)	0.0006	
<b>Key Secondary Endpoints</b>		
<b>Objective Response Rate</b>		
Patients with measurable disease	389	397
Number of patients with OR (%)	120 (30.8%)	173 (43.6%)
Diff, (95% CI);	12.7% (6.0%, 19.4%)	
p-value (Mantel-Haenszel chi-squared test*)	0.0002	

	<b>Lapatinib+Capecitabine N = 496</b>	<b>Kadcyla N = 495</b>
<b><i>Duration of Objective Response (months)</i></b>		
Number of patients with OR	120	173
Median	6.5	12.6

PFS: progression-free survival; OR: objective response

\* Stratified by: world region (United States, Western Europe, Other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs. > 1), and visceral vs. non-visceral disease.

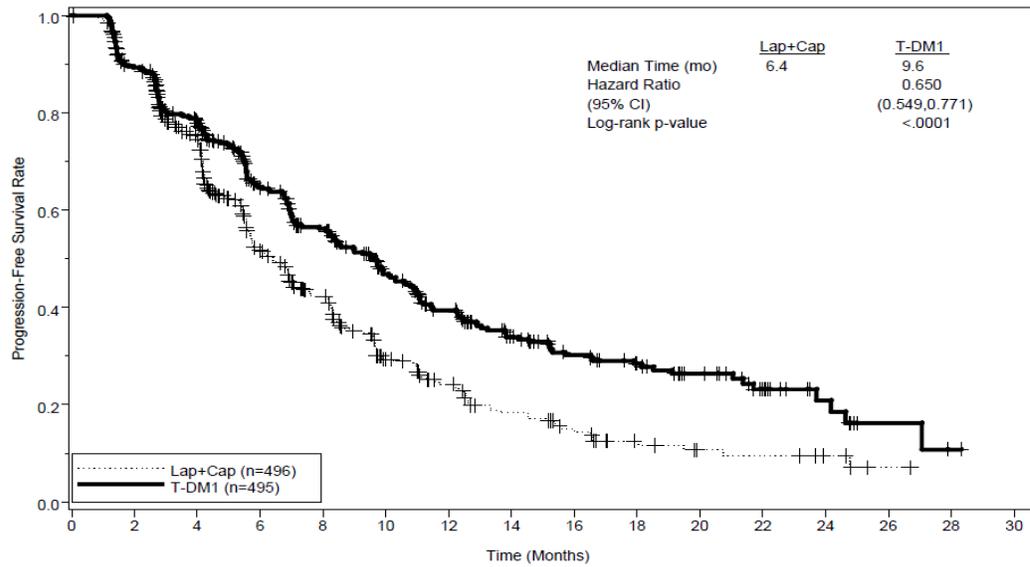
\*\* The first interim analysis of overall survival (OS) was performed at the time of primary PFS analysis. Strong treatment effect was observed, but pre-specified efficacy boundary was not crossed. A second interim analysis for OS was conducted when 331 OS events were observed and the results are presented in this table. The p-value met the O'Brien Fleming stopping boundary of the Lan Demets alpha spending function for the 2nd OS interim analysis (p = 0.0037).

A treatment benefit with Kadcyla in terms of PFS and OS was observed in most patient subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments. In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively; in patients with measurable disease the hazard ratios were 0.62 (95% CI: 0.52, 0.75) and 0.65 (95% CI: 0.51, 0.82), respectively. The PFS and OS hazard ratios in patients who were younger than 65 years old (n=853) were 0.62 (95% CI: 0.52, 0.74) and 0.66 (95% CI: 0.52, 0.83), respectively. In patients ≥ 65 years old (n=138), the hazard ratios for PFS and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively.

Pre-specified subgroup analyses utilizing non-visceral and visceral evaluations based solely on investigator judgment at the time of randomization revealed IRC-assessed PFS hazard ratios of 0.96 (95% CI: 0.71, 1.30) and 0.55 (95% CI: 0.45, 0.67) for the non-visceral and visceral disease subgroups, respectively. For OS, the hazard ratios were 1.05 (95% CI: 0.69, 1.61) and 0.59 (95% CI: 0.46, 0.76), respectively.

To examine the possibility that heterogeneity of assessment or other factors may have affected the subgroup analysis, post-hoc analyses were performed using consistent definition of visceral disease = lung, liver, pleural effusion and ascites and applied to the IRC assessments of disease. These analyses revealed IRC-assessed PFS hazard ratios of 0.69 (95% CI: 0.51, 0.95) and 0.64 (95% CI: 0.53, 0.78) for the non-visceral and visceral subgroups, respectively. The hazard ratios for OS were 0.59 (95% CI: 0.37, 0.94) and 0.73 (95% CI: 0.57, 0.94), respectively.

**Figure 1** Kaplan-Meier curve of IRC-assessed progression-free survival

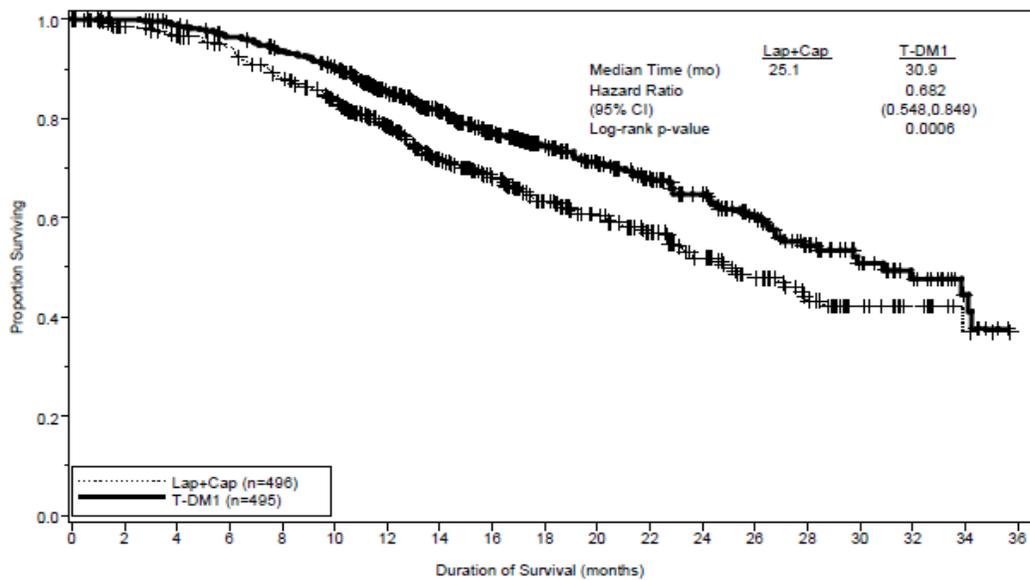


Number at Risk:

Lap+Cap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.  
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

**Figure 2** Kaplan-Meier curve of overall survival



Number at Risk:

Lap+Cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.  
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

### **Other MBC Clinical Studies**

A randomized, multicentre, open-label phase II, study (TDM4450g/BO21976) evaluated the effects of Kadcyła versus trastuzumab plus docetaxel in patients with HER2-positive MBC who had not received prior chemotherapy for metastatic disease. Patients were randomized to receive Kadcyła 3.6 mg/kg IV every 3 weeks (n=67) or trastuzumab 8 mg/kg IV loading dose followed by 6 mg/kg IV every 3 weeks plus docetaxel 75-100 mg/m<sup>2</sup> IV every 3 weeks (n=70).

The primary endpoint was PFS assessed by investigator. The median PFS was 9.2 months in the trastuzumab plus docetaxel arm and 14.2 months in the Kadcyła arm with a median follow-up of approximately 14 months in both arms. The ORR was 58.0% with trastuzumab plus docetaxel and 64.2% with Kadcyła. The median duration of response was not reached with Kadcyła vs. median duration 9.5 months in the control arm. The median OS was not reached in both arms.

A Phase II, single-arm, open-label study (TDM4374g) evaluated the effects of Kadcyła in patients with HER2-positive incurable locally advanced, or MBC. All patients were previously treated with HER2-directed therapies (trastuzumab and lapatinib), and chemotherapy (anthracycline, taxane, and capecitabine) in the neoadjuvant, adjuvant, locally advanced, or metastatic setting. The median number of anti-cancer agents that patients received in any setting was 8.5 (range, 5–19) and in the metastatic setting was 7.0 (range, 3–17), including all agents intended for the treatment of breast cancer.

Patients (n=110) received 3.6 mg/kg of Kadcyła intravenously every 3 weeks until disease progression or unacceptable toxicity.

The key efficacy analyses were ORR based on independent radiologic review and duration of objective response. The ORR was 32.7%, n=36 responders, by both IRC and investigator review. The median duration of response by IRC was not reached (4.6 months to not estimable).

A Phase II single-arm, open label study evaluated the effects of Kadcyła (TDM4258g) in patients with HER2-positive incurable LABC or MBC with a history of progression on HER2-directed therapy and at least one chemotherapy agent for MBC. Patients (n= 112) received Kadcyła administered at a dose of 3.6 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity for a maximum of 1 year.

The primary endpoint was ORR based on independent radiologic review. The administration of Kadcyła in patients with HER2-positive MBC previously treated with HER2-targeted therapy demonstrated single-agent activity with a confirmed ORR of 26.9%, as determined by the independent radiologic review, and a confirmed ORR of 38.9%, as assessed by the investigator. Kadcyła demonstrated anti-tumour activity in patients previously treated with both lapatinib and trastuzumab, with a confirmed ORR of 24.2% by independent radiologic review. The median duration of response by independent radiologic review assessment was not reached because of insufficient events and was 9.4 months per investigator assessment.

### **Early Breast Cancer (EBC)**

An overview of the study designs and demographic characteristics of patients enrolled in study BO27938 (KATHERINE) are presented in Table 14.

**Table 14 Summary of trial design and patient demographics for clinical trials in Early Breast Cancer (EBC)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
<b>Early Breast Cancer</b>					
BO27938 (KATHERINE)	Phase III, randomized, multicenter, multinational, two-arm, open label study	Trastuzumab: 6 mg/kg IV q3w for 14 cycles (8 mg/kg loading dose given if longer than 6 weeks since last dose of trastuzumab)  OR  Kadcyla: 3.6 mg/kg q3w IV for 14 cycles	Trastuzumab: 743 patients enrolled, 720 patients treated  Kadcyla: 743 patients enrolled, 740 patients treated	Trastuzumab: 49.2 (23 – 80)  Kadcyla: 49.0 (24 – 79)	Trastuzumab: Female: 740 (99.6%) Male: 3 (0.4%)  Kadcyla: Female: 741 (99.7%) Male: 2 (0.3%)

**Study Results in Early Breast Cancer (EBC)**

KATHERINE (BO27938) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer with residual invasive tumour in the breast and/or axillary lymph nodes following taxane and trastuzumab-based therapy as part of a neoadjuvant regimen before trial enrollment. Patients may have also received an anthracycline as part of neoadjuvant treatment. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumour samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio  $\geq 2.0$  determined at a central laboratory. Patients were randomized (1:1) to receive trastuzumab or Kadcyla. Randomization was stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluated after preoperative therapy.

Patients were excluded from the study if any of the following criteria were met: gross residual disease remaining after mastectomy or positive margins after breast-conserving surgery; progressive disease during neoadjuvant therapy; and cardiopulmonary dysfunction, including heart failure of New York Heart Association (NYHA) class II (mild symptoms and function limitation) or higher or a history of a reduction in the left ventricular ejection fraction to < 40% with previous therapy.

Kadcyla was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with Kadcyla or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity, whichever occurred first. At the time of the primary analysis, median treatment duration was 10 months (range: 1–12) for Kadcyla, and median treatment

duration was 10 months (range: 1–13) for trastuzumab. Patients who discontinued Kadcyla could complete the duration of their intended study treatment up to 14 cycles of HER2-directed therapy with trastuzumab, if appropriate, based on toxicity considerations and investigator discretion.

The primary efficacy endpoint of the study was Invasive Disease Free Survival (IDFS). IDFS was defined as the time from the date of randomization to first occurrence of ipsilateral invasive breast tumour recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional endpoints included IDFS including second primary non-breast cancer, disease free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI).

**Table 15 Patient Demographics BO27938 (KATHERINE) study**

	<b>trastuzumab N = 743</b>	<b>Kadcyla N = 743</b>
<b>Age (years)</b>		
Median	49	49
Range	23-80	24-79
<b>Sex, n (%)</b>		
Female	740 (99.6)	741 (99.7)
Male	3 (0.4)	2 (0.3)
<b>Race, n (%)</b>		
Caucasian	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
American Indian or Alaska Native	50 (6.7)	36 (4.8)
Black or African American	19 (2.6)	22 (2.8)
Other	79 (10.6)	70 (9.4)
<b>Region, n (%)</b>		
North America	164 (22.1)	170 (22.9)
Western Europe	403 (54.2)	403 (54.2)
Rest of World	176 (23.7)	170 (22.9)
<b>ECOG Performance status, n (%)</b>		
0	613 (82.5)	597 (80.3)
1	130 (17.5)	146 (19.7)
<b>Hormone-receptor status (eCRF), n (%)</b>		
Positive (ER and/or PgR positive)	540 (72.7)	534 (71.9)
Negative (ER negative and PgR negative/unknown)	203 (27.3)	209 (28.1)
<b>Preoperative HER2-directed therapy (eCRF), n (%)</b>		
Trastuzumab only	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-directed therapy	147 (19.8)	143 (19.2)
<b>Preoperative Pertuzumab (eCRF), n (%)</b>		
Received pertuzumab	139 (18.7)	133 (17.9)
Did not receive pertuzumab	604 (81.3)	610 (82.1)
<b>Prior Anthracycline received, n (%)</b>		
Received prior anthracycline	564 (75.9)	579 (77.9)
Did not receive prior anthracycline	179 (24.1)	164 (22.1)

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen and 19.5% of patients received another HER2-targeted agent in

addition to trastuzumab as a component of neoadjuvant therapy. Pertuzumab was the second therapy in 93.8% of patients who received a second neoadjuvant HER2-directed agent.

A clinically meaningful and statistically significant improvement in IDFS was observed in patients who received Kadcyła compared with trastuzumab (HR = 0.50, 95% CI [0.39, 0.64],  $p < 0.0001$ ), corresponding to a 50% reduction in risk of an IDFS event. Estimates of 3-year event-free rates were 88.3% vs. 77.0% in Kadcyła vs. trastuzumab arms, respectively. See Table 16 and Figure 3.

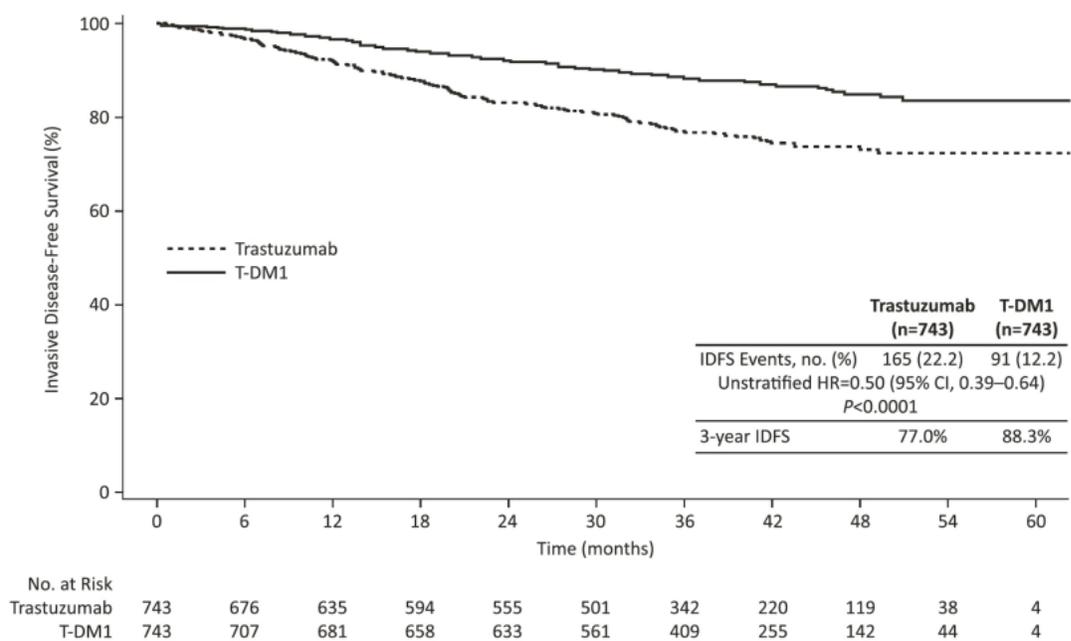
**Table 16 Summary of Efficacy from BO27938 (KATHERINE) study**

	<b><u>Trastuzumab</u></b> <b><u>N = 743</u></b>	<b><u>Kadcyła</u></b> <b><u>N = 743</u></b>
<b><u>Primary Endpoint</u></b>		
<b><u>Invasive Disease Free Survival (IDFS)</u></b>		
Number (%) of patients with event	165 (22.2%)	91 (12.2%)
HR [95% CI]	0.50 [0.39, 0.64]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate <sup>1</sup> , % [95% CI]	77.0 [73.78, 80.26]	88.3 [85.81, 90.72]

**Key to abbreviations (Table 16):** HR: Hazard Ratio; CI: Confidence Intervals.

1. 3-year event-free rate derived from Kaplan-Meier estimates

**Figure 3 Kaplan-Meier Curve of Invasive Disease Free Survival in BO27938 (KATHERINE)**



In BO27938 (KATHERINE), consistent treatment benefit of Kadcyła for IDFS was seen in all the pre-specified subgroups evaluated, supporting the robustness of the overall results. The primary IDFS analysis is also supported by secondary outcome measures. More patients treated with trastuzumab vs. Kadcyła experienced a disease-free survival (DFS) event (23% vs. 13%; HR = 0.53). More patients treated with trastuzumab vs. Kadcyła experienced an IDFS including second primary non-breast cancer event (22.5% vs. 12.4%, HR = 0.51). Distant recurrence as the first invasive event occurred in 16% of trastuzumab vs. 10.5% of Kadcyła treated patients (HR = 0.60).

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

Trastuzumab emtansine was generally well tolerated in rats (a nonbinding species) and cynomolgus monkeys (a relevant binding species) in single- and repeat-dose toxicity studies. The identified toxicities in both species were generally limited to findings consistent with the pharmacology of DM1 including hepatotoxicity, hematologic/bone marrow toxicity (including decreased platelet levels), lymphoid depletion in the spleen and thymus, neurotoxicity (monkeys only), reproductive toxicity (rats only) and increased numbers of mitotic figures in cells of epithelial and phagocytic origin.

### Single-Dose Toxicity Studies:

In rats, a single IV dose of trastuzumab emtansine resulted in mortality and morbidity at a dose of 60 mg/kg. Animals had body weight loss, evidence of hepatotoxicity, peripheral granulocytosis, and decreased platelet levels. Males had adverse effects in the testicle and epididymis, including degeneration of seminiferous tubules with hemorrhage in the testes associated with increased weights of testes and epididymides at a severely toxic dose level (60 mg/kg; about 4 times the clinical exposure based on AUC), and females had hemorrhage and necrosis of the corpus luteum in ovaries. Trastuzumab emtansine doses of 6 and 20 mg/kg were tolerated with no adverse clinical signs; the target organs affected were comparable to those affected at 60 mg/kg with the exception of changes to the male and female reproductive organs, and with less severity. In cynomolgus monkeys, a single IV dose of trastuzumab emtansine was well tolerated following administration of 3, 10, or 30 mg/kg with evidence of hepatotoxicity and decreased platelet levels observed at 30 mg/kg. The toxicity of DM1 was also investigated in rats. A single IV dose was tolerated up to 0.2 mg/kg. With the exception of axonal degeneration which was observed only in monkeys, the toxicities observed after administration of DM1 were comparable to those observed in rats and monkeys administered trastuzumab emtansine.

The findings from the single-dose toxicity studies with trastuzumab emtansine and DM1 are summarized in Table 17.

### Repeat-Dose Toxicity Studies:

In cynomolgus monkeys, IV administration of trastuzumab emtansine every three weeks for 4 or 8 doses at 3, 10, and 30 mg/kg, and 1, 3, and 10 mg/kg, respectively, followed by a 3- or 6-week recovery period, was well tolerated at all dose levels evaluated, with no signs of overt toxicity. The main toxicologic findings attributed to treatment with trastuzumab emtansine were comparable across both studies, and included hepatotoxicity, lymphoid depletion in the spleen and thymus, microscopic changes in the lacrimal glands, and irreversible axonal degeneration in the sciatic nerve and spinal cord. Based on the mechanism of action of the cytotoxic component DM1, there is clinical potential for neurotoxicity. Decreases in weights of the epididymides, prostate, testes, seminal vesicles, and uterus were also observed, but the interpretation of these results is unclear due to the varied sexual maturity of enrolled animals. The findings from the repeat-dose toxicity studies with trastuzumab emtansine are summarized in Table 18.

**Carcinogenicity:**

No carcinogenicity studies have been performed to establish the carcinogenic potential of Kadcyła.

**Genotoxicity:**

In a rat bone marrow micronucleus assay, DM1 was positive for micronuclei formation after a single low dose in the DM1 concentration range measured in humans given trastuzumab emtansine, confirming that Kadcyła is an aneugen and/or clastogen. No evidence of mutagenic activity was observed in an *in vitro* bacterial reverse mutation assay of DM1. In an *in vitro* micronucleus assay of trastuzumab emtansine in cynomolgus monkeys, no evidence of chromosomal damage to bone marrow cells was observed. The findings from the mutagenicity studies are summarized in Table 19.

**Reproductive and Developmental Toxicology:**

Dedicated embryo-fetal development studies have not been conducted in animals with trastuzumab emtansine. Developmental toxicity of trastuzumab has been identified in the clinical setting although it was not predicted in the non-clinical program. In addition, developmental toxicity of maytansine has been identified in non-clinical studies which suggests that DM1, the microtubule-inhibiting cytotoxic maytansinoid drug component of trastuzumab emtansine, will be similarly teratogenic and potentially embryotoxic.

No fertility studies in animals have been performed to evaluate the effect of Kadcyła. However, based on results from general animal toxicity studies, adverse effects on fertility can be expected (see Single-Dose Toxicity Studies and Repeat-Dose Toxicity Studies).

**Special Toxicology:**

Specific toxicity studies conducted with trastuzumab emtansine and DM1 include: *in vitro* hERG assay in human embryonic kidney (HEK293) cell, a cardiovascular safety pharmacology study in cynomolgus monkeys, an *in vitro* hemolytic potential and blood compatibility, a tissue cross-reactivity and a bridging study in cynomolgus monkeys. Details from these studies are provided in Table 20.

**Table 17 Single-Dose Toxicity Studies**

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg) <sup>a</sup>	Duration of Dosing
04-1214-1459	Single-Dose Toxicity	Rat/Sprague-Dawley	10/M, 10/F	IV	trastuzumab emtansine: 6, <u>20</u> , 60	NA
Comments: Trastuzumab emtansine was not tolerated in rats administered a single IV dose of 60 mg/kg based on clinical signs, body weight loss, and high rate of morbidity/mortality.						
04-0976-1459	Single-Dose Toxicity	Cynomolgus Monkey <sup>b</sup>	6/M, 6/F	IV	trastuzumab emtansine: 3, 10, <u>30</u>	NA
Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg. Adverse effects on the liver and decreased platelet levels that were observed at 30 mg/kg were reversible after a 3-week recovery period. The HNSTD was 30 mg/kg.						
05-1191	Single-Dose Toxicity	Rat/Sprague-Dawley	10/M, 10/F	IV	DM1: 0.05, 0.1, <u>0.2</u>	NA
Comments: DM1 was well tolerated in rats up to 0.2 mg/kg. Effects on the liver, platelets, and lymphoid organs were comparable to those observed in rats and monkeys administered trastuzumab emtansine, and were reversible after a 3-week recovery period. The HNSTD was 0.2 mg/kg.						

IV= intravenous; NA- not applicable

<sup>a</sup> Unless otherwise specified.

<sup>b</sup> *Macaca fascicularis*.

The highest non-severely toxic dose (HNSTD) for each study is denoted by underline

**Table 18 Repeat-Dose Toxicity Studies**

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg) <sup>a</sup>	Duration of Dosing
04-0977-1459	Repeat-Dose Toxicity	Cynomolgus monkey <sup>b</sup>	7/M, 7/F	IV	Trastuzumab emtansine: 3, <u>10</u> , 30	Four doses (one dose every three weeks)
<p>Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg with no overt signs of toxicity. Notable trastuzumab emtansine-related changes at 10 and 30 mg/kg consisted primarily of increases in serum liver enzymes and decreases in red-cell mass and platelets.</p>						
07-0653	Repeat-Dose Toxicity	Cynomolgus monkey <sup>b</sup>	6/M, 6/ F	IV	Trastuzumab emtansine: 1, 3, <u>10</u>	Eight doses (one dose every three weeks)
<p>Comments: Trastuzumab emtansine was well tolerated up to 10 mg/kg. Notable trastuzumab emtansine-related changes at 10 mg/kg consisted primarily of increases in serum liver enzymes and decreases in red-cell mass and platelets. Overall, the findings observed between the first and last dose cycle in this study were comparable, indicating that chronic dosing of trastuzumab emtansine did not result in cumulative toxicities.</p>						

IV=intravenous

<sup>a</sup> Unless otherwise specified.

<sup>b</sup> *Macaca fascicularis*.

The highest non-severely toxic dose (HNSTD) for each study is denoted by underline

**Table 19 Mutagenicity Studies**

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg) <sup>a</sup>	Duration of Dosing
09-2654	<i>In vitro</i>	<i>Salmonella – Escherichia coli</i>	NA <sup>b</sup>	<i>In vitro</i>	DM1: 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate	NA
Comments: Results indicated DM1 was negative in the <i>Salmonella–Escherichia coli</i> /Mammalian-Microsome Reverse Mutation Assay under the conditions of this study						
09-2726	<i>In vivo</i>	Rat/Sprague-Dawley	5M, 5F	<i>In vivo</i>	DM1: 0.01, 0.05, 0.1, and 0.2	Single dose
Comments: DM1 induced a dose-dependent increase in micronucleus frequency at 0.05, 0.1, and 0.2 mg/kg, demonstrating evidence of aneugenicity and/or clastogenicity						
07-0653	<i>In vivo</i>	Cynomolgus Monkey <sup>b</sup>	6/M, 6/ F	IV	Trastuzumab emtansine: 1, 3, 10	21 Weeks
Comments: there was no evidence of micronuclei induction in bone marrow collected 7 days after the last dose.						

IV= intravenous; NA= not applicable

<sup>a</sup> Unless otherwise specified.

<sup>b</sup> *Macaca fascicularis*.

**Table 20 Special Toxicity Studies**

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Doses (mg/kg) <sup>a</sup>	Duration of Dosing
09-0234	hERG Assay	Human embryonic kidney (HEK293) cell	NA	<i>In vitro</i>	DM1: 2.6, 8.8, and 29.5 µM	NA
<p>Comments: DM1 inhibited hERG potassium current by (Mean ± SEM; n = 3) 0.3 ± 0.6% at 2.6 µM, 1.0 ± 0.5% at 8.8 µM and 2.5 ± 0.4% at 29.5 µM versus 0.6 ± 0.3% in control. IC20 and IC50 were estimated to be greater than 29.5 µM.</p>						
04-1031-1605	Cardiovascular Safety Pharmacology	Cynomolgus Monkey <sup>b</sup>	4/F	IV	Trastuzumab emtansine: 3, 10, 30	Single dose
<p>Comments: Trastuzumab emtansine did not affect ECG parameters, including QT/QTc. At 30 mg/kg trastuzumab emtansine, modest increases in systolic, diastolic, and mean arterial pressures were observed. Changes were most consistently observed on Day 5 post-dose, but were variable in onset and duration in individual monkeys.</p>						
04-1257-1459	Hemolytic Potential and Blood Compatibility	Cynomolgus monkey and human blood, serum, and plasma	NA	<i>In vitro</i>	Trastuzumab emtansine: 0, 1.25, 2.5, or 5 mg/mL	NA
<p>Comments: Hemolytic potential: no trastuzumab emtansine-related hemolysis in human and monkey serum and plasma. Blood and plasma compatibility: Trastuzumab emtansine compatible in human and monkey blood and plasma.</p>						
04-1215-1605	Tissue Cross-Reactivity	Cynomolgus monkey and human tissue	NA	<i>In vitro</i>	Trastuzumab emtansine: 1.0 or 10.0 µg/mL	NA
<p>Comments: Trastuzumab emtansine-specific binding observed at 1.0 and 10.0 µg/mL in both human and cynomolgus monkey tissues, and consisted primarily of epithelial, spindle, glial, and mononuclear cell staining in several tissues. Binding in monkey tissues was similar to that of human tissues yet less prevalent.</p>						
05-0848	Bridging Study	Cynomolgus monkey <sup>b</sup>	3/M, 3/F	IV	Trastuzumab emtansine: 3, 5%–7% UM 10, 5%–7% UM 30, 5%–7% UM	Single dose
<p>Comments: Trastuzumab emtansine was well tolerated up to 30 mg/kg. Body weight loss (females), adverse effects on the liver and decreased platelet levels observed at 30 mg/kg were reversible after a 3-week recovery period. Minimal non-reversible axonal degeneration in the sciatic nerve was observed at 30 mg/kg.</p>						

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IV= intravenous; NA= not applicable; UM= Unconjugated Maytansinoid

<sup>a</sup> Unless otherwise specified.

<sup>b</sup> *Macaca fascicularis*.

The highest non-severely toxic dose (HNSTD) for each study is denoted by underline

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

**PrKADCYLA®**  
**trastuzumab emtansine**

Read this carefully before you start taking Kadcyła and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Kadcyła.

**Serious Warnings and Precautions**

- **Medication Errors:** There is a risk of Kadcyła overdose due to medication errors. Verify with the healthcare professional that the authorized Kadcyła (trastuzumab emtansine) dose and NOT trastuzumab is used.
- **Liver Problems:** Kadcyła can cause inflammation and damage to liver cells. Severe liver damage may result in liver failure and death. To monitor liver problems, your blood will be checked regularly for increases in levels of liver enzymes.
- **Heart Problems:** Kadcyła can weaken the heart muscle leading to problems pumping the blood around your body and causing shortness of breath at rest, chest pain, swollen ankles or arms, and a sensation of rapid or irregular heartbeats. Your heart function will be checked before and regularly during treatment.
- **Bleeding Problems:** Platelets in the blood help blood clot. Kadcyła can lower the number of platelets in your blood and cause life-threatening bleeding. In some cases, bleeding has been fatal. The risk of bleeding is increased when taking Kadcyła with other medications used to thin your blood or prevent blood clots. Your doctor should provide additional monitoring if you are taking one of these other drugs.
- **Lung problems:** Kadcyła can cause lung problems, including inflammation (swelling) of the lung tissue, leading to lung failure and death.
- **Embryo-fetal toxicity (Harm to Unborn Baby):** Kadcyła can cause harm to the fetus (unborn baby), or death of the fetus, when taken by a pregnant woman. Women who could become pregnant need to use two effective birth control methods during Kadcyła treatment and for at least 7 months after treatment with Kadcyła.

**What is Kadcyła used for?**

Kadcyła pronounced “Kad-s(eye)-la” is used to treat people with breast cancer when:

- the cancer cells produce a large amount of HER2 proteins - your healthcare provider will test your cancer for this
- you have already received the medicine trastuzumab separately or in combination with a chemotherapy medicine from the class called taxane e.g. paclitaxel or docetaxel

- the cancer has spread to areas near the breast or to other parts of your body (metastasized)
- the cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy)

### **How does Kadcyła work?**

Kadcyła is made up of two types of medicine that are linked together. One part belongs to a group of medicines called monoclonal antibodies (trastuzumab) and the other belongs to a group of medicines called anti-mitotics (DM1).

Kadcyła recognizes the cancer cells in the body by attaching to HER2 proteins. When Kadcyła attaches to the HER2 cancer cells, it may slow or stop the growth of the cancer or may also kill the cancer cells. After Kadcyła attaches to HER2 proteins, it enters the cancer cells where it releases the anti-mitotic drug DM1. DM1 may also kill the cancer cells.

### **What are the ingredients in Kadcyła?**

Medicinal ingredients: trastuzumab and DM1

Non-medicinal ingredients: polysorbate 20, sodium hydroxide, succinic acid, and sucrose.

### **Kadcyła comes in the following dosage forms:**

Single-use vial containing either 100 mg or 160 mg of trastuzumab emtansine.

### **Do not use Kadcyła if:**

You are allergic to this drug, to any ingredients in the formulation (see 'What are the ingredients in Kadcyła'), or to a component of the container. If you are not sure, talk to your healthcare professional before you are given Kadcyła.

### **To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Kadcyła. Talk about any health conditions or problems you may have, including if you:**

- have ever had a serious infusion-related (allergic) reaction when treated with trastuzumab
- are receiving treatment with blood thinner medications
- have any history of liver problems. Your doctor will check your blood to test your liver function before and regularly during treatment.
- are pregnant, think you may be pregnant or are planning to have a baby.

### **Other warnings you should know about:**

Kadcyła can make some existing conditions worse, or cause side effects. See '[What are the possible side effects of using Kadcyła?](#)' below.

**Patients aged below 18 years:** Kadcyła should not be used in these patients as there is no information on how well it works and if it is safe to use in these younger patients.

**Pregnancy, breast-feeding and fertility:** Kadcyła is not recommended if you are pregnant. There is no information about the safety of Kadcyła in pregnant women. Kadcyła may affect fertility based on animal studies.

- Tell your doctor before using Kadcyła if you are pregnant, think you may be pregnant or are planning to have a baby.

- Use effective contraception to avoid becoming pregnant while you are being treated with Kadcyła. Also, use this contraception for 7 months after your last dose. Female partners of male patients should also use effective contraception. Talk to your healthcare provider about the best contraception for you.
- If you do become pregnant during treatment with Kadcyła, tell your healthcare provider straight away.

Do not breast-feed during treatment with Kadcyła and for 7 months after stopping treatment. It is not known whether the ingredients in Kadcyła pass into breast-milk. Talk to your doctor about this.

**Driving and using machines:** Kadcyła may impair your ability to drive or use machines by causing symptoms such as tiredness, headache, dizziness, and blurred vision. If you experience infusion-related reactions (e.g. flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing) do not drive and use machines until symptoms abate completely.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Kadcyła:**

**Tell your healthcare professional if you are taking, have recently taken or might take any other medicines.**

This includes medicines obtained without a prescription and herbal medicines. In particular, tell your healthcare professional if you are taking blood thinners.

**How to take Kadcyła:**

Kadcyła will be given to you by a healthcare professional in a hospital or clinic:

**Usual dose:**

- It is given by a drip into a vein (intravenous infusion) once every 3 weeks at a starting dose of 3.6 mg of Kadcyła for every kilogram of your body weight.
- The first infusion will be given to you over 90 minutes. You will be watched by a healthcare provider while it is being given and for at least 90 minutes following the initial dose, in case you have any side effects.
- If the first infusion is well tolerated, the infusion on your next visit may be given over 30 minutes. You will be watched by a healthcare provider while it is being given and for at least 30 minutes following the dose, in case you have any side effects.
- The total number of infusions that you will be given depends on how you respond to the treatment and which indication is treated.
- If you experience side effects, your doctor may decide to carry on your treatment but lower your dose, delay the next dose or stop the treatment.

**Overdose:**

If you think you have been given too much Kadcyła, tell your healthcare professional, hospital emergency department or regional poison control centre immediately even if there are no symptoms.

There is a risk of Kadcyła overdose due to medication errors. Verify with the healthcare professional that the authorized Kadcyła (trastuzumab emtansine) dose and NOT trastuzumab dose is used.

**Missed Dose:**

If you forget or miss your Kadcyła appointment, discuss this as soon as possible with your healthcare professional to make another appointment.

Do not stop having this medicine without talking to your healthcare professional first. If you have any further questions on the use of this medicine, ask your healthcare professional.

**What are possible side effects from using Kadcyła?**

Like all medicines, this medicine can cause unwanted effects. Tell your health care professional if you notice any of the side effects given below.

**Very common (may affect more than 1 in 10 people):**

- Jaundice
- Unexpected bleeding
- Tiredness
- Feeling sick (nausea, vomiting)
- Headache
- Muscle or joint pain
- Abdominal pain
- Constipation
- Nerve damage
- Diarrhea
- Dry mouth
- Swelling of the mouth
- Chills or flu like symptoms
- Difficulty sleeping
- Decrease in your potassium levels (shown in a blood test)
- Decreased red blood cells (shown in a blood test)

**Common (may affect up to 1 in 10 people):**

- Heart problems
- Allergic reactions during or following infusions
- Decreased white blood cells (shown in a blood test)
- Swollen mouth or eyelids
- Dry eyes, watery eyes or blurred vision
- Increase in blood pressure
- Dizziness
- Loss of taste
- Itching

- Breathing problems, including shortness of breath
- Memory loss

**Uncommon (may affect up to 1 in 100 people):**

- Kadcyła can cause a condition known as nodular regenerative hyperplasia of the liver. Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.

These are not all the possible side effects you may feel when taking Kadcyła. If you experience any side effects not listed here, contact your healthcare professional.

If you get any of the side effects after your treatment with Kadcyła has been stopped, talk to your doctor and tell them that you have been treated with Kadcyła.

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>VERY COMMON</b> Unexpected bleeding from the nose, gums	✓		
Your skin and whites of your eyes get yellow		✓	
<b>COMMON</b> Shortness of breath at rest, chest pain, swollen ankles or arms, sensation of rapid or irregular heartbeats		✓	
Tenderness or redness of your skin, pain, or swelling at the injection site. In rare cases, burning sensation, blistering and ulcerative injury can be developed		✓	
Flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, trouble swallowing		✓	
Tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet	✓		
Shortness of breath, cough with fever		✓	
<b>UNCOMMON</b>	✓		

Blood in stools, swelling of the abdomen			
<b>If you become pregnant</b>		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

- Kadcyła will be stored by the healthcare professionals at the hospital or clinic.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.
- Store vials in a refrigerator at 2-8°C.

When prepared as a solution for infusion, Kadcyła is stable for up to 24 hours at 2-8°C, and must be discarded thereafter. Do not use Kadcyła if you notice any particles or it is the wrong colour (see '[What dosage forms it comes in](#)').

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

### If you want more information about Kadcyła:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website; (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.rochecanada.com](http://www.rochecanada.com), or by calling 1-888-762-4388

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