AUSTRALIAN PRODUCT INFORMATION

Kadcyla® (trastuzumab emtansine)

WARNING: Do not substitute Kadcyla for or with trastuzumab or trastuzumab deruxtecan. In order to prevent medication errors, check the vial labels to ensure the medicine being prepared and administered is Kadcyla (trastuzumab emtansine) and not trastuzumab or trastuzumab deruxtecan.

1. NAME OF THE MEDICINE

trastuzumab emtansine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kadcyla is available as a single-use vial containing 100 mg or 160 mg of trastuzumab emtansine.

For the full list of excipients, *see section 6.1 List of excipients*.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Early Breast Cancer

Kadcyla, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Metastatic Breast Cancer

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

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients treated with Kadcyla should have HER2 positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) assessed by a validated test.

Kadcyla therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.

Do not substitute Kadcyla for or with trastuzumab or trastuzumab deruxtecan. In order to prevent medication errors, it is important to check the vial labels to ensure the medicine being prepared and administered is Kadcyla (trastuzumab emtansine) and not trastuzumab or trastuzumab deruxtecan.

In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded in the patient medical record.

Dosage
The recommended dose of Kadcyla is 3.6 mg/kg, administered as an intravenous (IV) infusion every 3 weeks (21-day cycle).

Duration of treatment
Patients with early breast cancer should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

Patients with metastatic breast cancer should receive treatment until disease progression or unmanageable toxicity.

Missed dose
If a planned dose of Kadcyla is missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the rate the patient tolerated the most recent infusion.

Method of Administration
For instructions on reconstitution and dilution of the product before administration, *see section 6.6 Special precautions for disposal and other handling.*

Kadcyla must be reconstituted and diluted by a healthcare professional and administrated as an IV infusion. Do not administer as an IV push or bolus.

Once the infusion solution is prepared, it should be administered immediately.

If 0.45% sodium chloride is used, the infusion can be administered without a 0.22 micron in-line polyethersulfone (PES) filter. If 0.9% sodium chloride is used, a 0.22 micron in-line PES filter is required for administration of the infusion.

If the infusion solution is not used immediately, the infusion solution can be stored for up to 24 hours at 2°C - 8°C (*see section 6.4 Special precautions for storage*).

Administer the initial dose as a 90 minute IV 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 Kadcyla administration (*see section 4.4 Special warnings and precautions for use; Extravasation)*.

If prior infusions were well tolerated, subsequent doses of Kadcyla may be administered as a 30 minute infusion and patients should be observed during the infusions and for at least 30 minutes after the infusion. The infusion rate of Kadcyla should be slowed or interrupted if the patient develops infusion-related symptoms (*see section 4.4 Special warnings and precautions for use; Infusion-Related Reactions, Hypersensitivity*). Discontinue Kadcyla for life-threatening infusion reactions.

Dosage adjustment

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

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 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2 Dose Modification Guidelines for Patients with Early Breast Cancer
(see section 4.4 Special warnings and precautions for use)

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 Kadcyla until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue Kadcyla
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 to ≤ 5 × ULN on day of scheduled treatment)	Do not administer Kadcyla 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 Kadcyla until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue Kadcyla

Adverse reaction	Severity	Treatment modification
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0 × the ULN on day of scheduled treatment	Do not administer Kadcyla until total bilirubin recovers to ≤ 1.0 × ULN, and then reduce one dose level
	TBILI > 2 × ULN at any time	Discontinue Kadcyla
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to < 75,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), 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^3	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.
Left Ventricular Dysfunction	LVEF < 45%	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue Kadcyla.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer Kadcyla Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue Kadcyla.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with Kadcyla.
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF < 45%	Discontinue Kadcyla.
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution ≤ Grade 2.

Adverse reaction	Severity	Treatment modification
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyla.
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue Kadcyla if not resolving with standard treatment.
	Grade 3-4	Discontinue Kadcyla.

ALT: alanine transaminase, AST: aspartate transaminase, CHF: congestive heart failure, LVEF: left ventricular ejection fraction, LVSD: left ventricular systolic dysfunction, TBILI: Total Bilirubin, ULN: upper limit of normal
*Prior to starting Kadcyla treatment.

Table 3 Dose Modification Guidelines for Patients with Metastatic Breast Cancer
(see section 4.4 Special warnings and precautions for use)

Adverse reaction	Severity	Treatment modification
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 Kadcyla until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level.
	Grade 4 (> 20 × the ULN)	Discontinue Kadcyla.
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3 × the ULN)	Do not administer Kadcyla 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 Kadcyla until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10 × the ULN)	Discontinue Kadcyla.
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN	Permanently discontinue Kadcyla in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication.
Thrombocytopenia	Grade 3 (25,000 to < 50,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level.
	Grade 4 (< 25,000/mm^3)	Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.
	Symptomatic CHF	Discontinue Kadcyla.
	LVEF < 40%	Do not administer Kadcyla.

Adverse reaction	Severity	Treatment modification
Left Ventricular Dysfunction		Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue Kadcyla.
	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue Kadcyla.
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.
	LVEF > 45%	Continue treatment with Kadcyla.
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue Kadcyla
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution Grade ≤ 2

ALT: alanine transaminase, AST: aspartate transaminase, DILI: Drug Induced Liver Injury, LVEF: left ventricular ejection fraction, NRH: Nodular regenerative hyperplasia, ULN: upper limit of normal

Special populations

Elderly

There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older. No dose adjustment of Kadcyla is required in patients aged ≥ 65 years (*see section 4.4 Special warnings and precautions for use; Use in the Elderly*).

Renal impairment

No adjustment to the starting dose of Kadcyla is needed in patients with mild or moderate renal impairment (*see section 5.2 Pharmacokinetic properties; Pharmacokinetics in Special Populations*). 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 is required for patients with mild or moderate hepatic impairment (*see section 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations*). 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 section 4.4 Special warnings and precautions for use; Hepatotoxicity*).

Paediatric population

The safety and efficacy of Kadcyla in children below 18 years of age have not been established.

4.3 CONTRAINDICATIONS

Kadcyla is contraindicated in patients with a known hypersensitivity to Kadcyla or any of its excipients (see section 4.4 Special warnings and precautions for use; Infusion-Related Reactions and Hypersensitivity Reactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Patients treated with Kadcyla must have confirmed HER2-positive tumour status as assessed by either HER2 protein over-expression or gene amplification.

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 Kadcyla *(see section 4.8 Adverse effects (Undesirable effects))*. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates.

It is recommended that treatment with Kadcyla be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where Kadcyla should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment (*see section 4.2 Dose and method of administration*).

Patients with dyspnoea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events.

Hepatotoxicity

Serious hepatotoxicity has been reported, including liver failure and death, in patients treated with Kadcyla. Hepatotoxicity has been observed predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis) in clinical trials *(see section 4.8 Adverse effects (Undesirable effects))*. 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 Kadcyla on transaminases has also been observed. Patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of Kadcyla in the majority of the cases. Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some with a fatal outcome due to drug-induced liver injury have been observed in patients treated with Kadcyla in clinical trials. Observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential.

Monitor serum transaminases and bilirubin prior to initiation of Kadcyla treatment and prior to each Kadcyla dose. Reduce the dose or discontinue Kadcyla as appropriate in cases of increased serum transaminases and/or total bilirubin *(see section 4.2 Dose and method of administration; Dose adjustments*). Kadcyla has not been studied in patients with serum transaminases > 2.5 x ULN (upper limit of normal) or total bilirubin > 1.5 x ULN prior to initiation of treatment, except in a dedicated pharmacology study of the use of Kadcyla in hepatic impairment (*see section 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations*). Two out of ten patients with mild hepatic impairment withdrew from the study due to increased levels of bilirubin, and one patient with moderate hepatic impairment developed fatal hepatic

encephalopathy, considered to be at least partly related to trastuzumab emtansine. Permanently discontinue Kadcyla treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN.

Cases of NRH of the liver have been identified from liver biopsies in patients treated with Kadcyla. NRH is a rare liver condition characterised 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, Kadcyla treatment must be permanently discontinued.

Left Ventricular Dysfunction

Kadcyla may lead to reductions in left ventricular ejection fraction (LVEF). LVEF < 40% has been observed in patients treated with Kadcyla. Symptomatic congestive heart failure (CHF) is a potential risk. In the phase III study TDM4370g/BO21977 (EMILIA), left ventricular dysfunction occurred in 1.8% of patients in the Kadcyla-treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group *(see section 4.8 Adverse effects (Undesirable effects)).*

Assess LVEF (echocardiogram or multigated acquisition (MUGA) scanning) prior to initiation and at regular intervals (e.g. every three months) during treatment with Kadcyla to ensure LVEF is within the institution's normal limits.

Events of LVEF drop of >10% from baseline and/or CHF were observed in approximately 22% of patients with MBC in an observational study (BO39807) with baseline LVEF of 40-49% in a real world setting. Most of these patients 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.

Specific guidelines regarding dose modifications and discontinuation are provided in *section 4.2 Dose and method of administration; Dosage adjustments*.

Infusion-Related Reactions

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

Infusion-related reactions, characterised by one or more of the following symptoms - flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia -have been reported in clinical trials of Kadcyla. In general, these symptoms were not severe *(see section 4.8 Adverse effects (Undesirable effects)).* In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Kadcyla treatment should be interrupted in patients with severe IRR. Kadcyla treatment should be permanently discontinued in the event of a life threatening infusion-related reaction (*see section 4.2 Dose and method of administration; Dosage adjustments*).

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 Kadcyla. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Haemorrhage

Cases of haemorrhagic events, including central nervous system, respiratory, and gastrointestinal haemorrhage, have been reported with Kadcyla treatment. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulation therapy or antiplatelet therapy; in others there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was reported in patients in clinical trials of Kadcyla. The majority of these patients had Grade 1 or 2 events ($\geq 50{,}000/mm^3$), with the nadir occurring by day 8 and generally improving to grade 0 or 1 ($\geq 75{,}000/mm^3$) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

In the phase III study TDM4370g/BO21977 (EMILIA) in patients with metastatic breast cancer, the overall frequency of thrombocytopenia was 31.2% in the Kadcyla-treated group and 3.3% in the lapatinib plus capecitabine-treated group (*see section 4.8 Adverse effects (Undesirable effects)*). The incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the Kadcyla-treated group and 0.4% in the lapatinib plus capecitabine-treated group. In Asian patients, the incidence of ≥ Grade 3 thrombocytopenia was 45.1% in the Kadcyla-treated group and 1.3% in the lapatinib plus capecitabine-treated group.

Thrombocytopenia was reported in 28.5% of early breast cancer patients treated with Kadcyla in study BO27938 (KATHERINE). Independent of race, the incidence of Grade 3 or 4 events ($< 50{,}000/mm^3$) was 5.7% in the Kadcyla-treated group. The overall frequency of thrombocytopenia in Asian patients in the Kadcyla-treated group in study BO27938 (KATHERINE) was 50.0% and that of Grade 3 or 4 thrombocytopenia was 18.8%.

Patients with thrombocytopenia ($< 100{,}000/mm^3$) and patients on anti-coagulant treatment should be monitored closely while on Kadcyla treatment. It is recommended that platelet counts are monitored prior to each Kadcyla dose. Rare cases of severe and prolonged thrombocytopenia (≥ Grade 3 thrombocytopenia lasting for more than 90 days) have been reported with Kadcyla. In most of these cases, patients received concomitant recombinant human thrombopoietin (rhTPO). Kadcyla has not been studied in patients with platelet counts $\leq 100{,}000/mm^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($< 50{,}000/mm^3$), do not administer Kadcyla until platelet counts recover to Grade 1 ($\geq 75{,}000/mm^3$). Please see *section 4.2 Dose and method of administration; Dosage adjustments*.

Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of Kadcyla. Treatment with Kadcyla should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

In the phase III study TDM4370g/BO21977 (EMILIA) in patients with metastatic breast cancer, the overall incidence of peripheral neuropathy was 23.3% and 3.1% for Grade ≥ 3.

In patients with early breast cancer in study BO27938 (KATHERINE), the overall incidence was 32.3% and 1.6% for Grade ≥ 3. Onset of the Grade 3 event of peripheral neuropathy ranged between Study Day 2 and Day 229, with a median of 60 days. In 50% of patients who experienced Grade 3 peripheral neuropathy, these events had resolved at the time of the primary IDFS analysis, while events were resolving in 25% of the patients.

Extravasation

In Kadcyla clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised of 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, very rare cases of epidermal injury or necrosis following extravasation have been observed within days to a few weeks after infusion *(see Section 4.8 Adverse Effects (Undesirable effects)*). Specific treatment for Kadcyla extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration. If extravasation occurs the infusion should be terminated immediately and the patient should be examined regularly as necrosis may occur within days to weeks after infusion.

Use in hepatic impairment

Please see section 5.2 Pharmacokinetic properties; Pharmacokinetics in Special Populations.

Use in renal impairment

No formal studies of Kadcyla in patients with renal impairment have been conducted (*see Section 5.2 Pharmacokinetic properties; Pharmacokinetics in Special Populations)*.

Use in the Elderly

There are insufficient data to establish the safety and efficacy of Kadcyla in patients 75 years of age or older (*see section 5.1 Pharmacodynamic properties; Clinical Trials; TDM4370g/BO21977 (EMILIA)*). Based on a population pharmacokinetic analysis, age does not affect the pharmacokinetics of Kadcyla.

Paediatric use

The safety and efficacy of Kadcyla in children below 18 years of age have not been established.

Effects on laboratory tests

Please see section 4.4 Special warnings and precautions for use; Hepatotoxicity and Thrombocytopenia.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies with Kadcyla in humans have been conducted.

In vitro metabolism studies in human liver microsomes suggest that DM1, the cytotoxic component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and, to a lesser extent, by CYP3A5. DM1 does not induce or inhibit P450-mediated metabolism *in vitro.* Plasma DM1 concentrations may be affected by CYP3A4/5 inhibitors or inducers. Thus, patients who are receiving strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin) concomitantly with trastuzumab emtansine should be closely monitored for adverse reactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effects of trastuzumab emtansine on human fertility are unknown. No dedicated fertility studies have been conducted with trastuzumab emtansine. However, based on results from rat toxicity studies, adverse effects on fertility may occur.

Single-dose toxicity studies of trastuzumab emtansine in rats demonstrated adverse effects on reproductive organs. Male rats exhibited degeneration of seminiferous tubules in the testes and luminal debris in the epididymides at 60 mg/kg (approximately 9-times the anticipated clinical trastuzumab emtansine exposure, based on AUC). At the same dose in female rats, haemorrhage and necrosis of the corpus luteum in the ovaries and mammary gland degeneration and necrosis was observed. Mammary gland degeneration and necrosis was also observed in males at doses from 20 mg/kg (3-fold the anticipated clinical trastuzumab emtansine exposure, based on AUC).

Use in pregnancy (Category D)

Trastuzumab emtansine can result in embryo-foetal death or birth defects when administered to a pregnant woman. There are no clinical studies of trastuzumab emtansine in pregnant women. No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. Trastuzumab, a component of trastuzumab emtansine, can cause foetal harm or death when administered to pregnant women. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. DM1, the cytotoxic component of trastuzumab emtansine, is a microtubule inhibitory drug derived from maytansine. Based on animal studies of maytansine, DM1, is expected to be teratogenic and potentially embryotoxic.

Administration of trastuzumab emtansine to pregnant women is not recommended. Women of child bearing potential and female partners of male patients of child bearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months following the last dose of trastuzumab emtansine. Women who become pregnant must contact their doctor and should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended.

Use in lactation

It is not known whether trastuzumab emtansine is excreted in human breast milk.

However, trastuzumab was shown to be readily transferred through the placenta (foetal amniotic fluid and sera samples around 20-30% of maternal plasma concentrations), with a small amount (2% of maternal plasma concentrations) excreted in the milk of monkeys after IV doses of 25 mg/kg for 4 consecutive days from gestation day 120 followed by twice weekly until post-partum day 28.

Since many drugs are excreted in human breast milk, and because of the potential for serious adverse reactions in nursing infants from trastuzumab emtansine, women should discontinue nursing prior to initiating treatment with trastuzumab emtansine. Women may begin nursing 7 months following the last dose of Kadcyla.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

On the basis of reported adverse reactions, Kadcyla has no or negligible influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing infusion-related reactions (flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat) should be advised not to drive and use machines until symptoms abate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Early Breast Cancer

The safety of Kadcyla has been evaluated in 740 patients with early breast cancer in Study BO27938 KATHERINE. Adverse drug reactions from KATHERINE (**Table 4**) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 4 Adverse drug reactions occurring in patients treated with Kadcyla in Study BO27938 (KATHERINE)

System Organ Class	All grades (%) n = 740	Grade 3 - 5 (%) n = 740	Frequency Category
Blood and Lymphatic System Disorders			
Thrombocytopenia	28.6	5.7	very common
Anaemia	10.1	1.1	very common
Neutropenia	8.2	1.4	common
Cardiac Disorders			
Left ventricular dysfunction	3.0	0.5	common
Eye Disorders			
Lacrimation increased	5.5	0	common
Dry eye	4.5	0	common
Vision blurred	3.9	0	common
Conjunctivitis	3.5	0	common
Gastrointestinal Disorders			
Nausea	41.6	0.5	very common
Constipation	16.9	0.1	very common

System Organ Class	All grades (%) n = 740	Grade 3 - 5 (%) n = 740	Frequency Category
Stomatitis	15.1	0.1	very common
Vomiting	14.7	0.5	very common
Dry Mouth	13.5	0.1	very common
Diarrhoea	12.3	0.8	very common
Abdominal pain	10.7	0.4	very common
Dyspepsia	4.5	0	common
General Disorders and Administration site conditions			
Fatigue	49.1	1.1	very common
Pyrexia	10.4	0	very common
Chills	5.3	0	common
Oedema peripheral	3.9	0	common
Asthenia	0.4	0	uncommon
Hepatobiliary Disorders			
Nodular regenerative hyperplasia	0.3	0.3	uncommon
Immune System Disorders			
Drug hypersensitivity	2.7	0.4	common
Injury, Poisoning, and Procedural Complications			
Infusion related reaction	1.6	0	common
Radiation pneumonitis	1.6	0.3	common
Investigations			
Transaminases increased	32.6	1.6	very common
Blood alkaline phosphatase increased	8.2	0	common
Blood bilirubin increased	6.6	0	common
Metabolism and Nutrition Disorders			
Hypokalaemia	6.8	1.2	common
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal pain	29.5	0.7	very common
Arthralgia	27.3	0.1	very common
Myalgia	15.3	0.4	very common
Nervous System Disorders			
Headache	28.2	0	very common
Neuropathy peripheral	27.7	1.6	very common
Dizziness	9.5	0.1	common

System Organ Class	All grades (%) n = 740	Grade 3 - 5 (%) n = 740	Frequency Category
Dysgeusia	7.7	0	common
Psychiatric Disorders			
Insomnia	13.6	0	very common
Infections and Infestations			
Urinary tract infection	10.4	0.4	very common
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	21.5	0	very common
Cough	13.5	0.1	very common
Dyspnoea	8.4	0.1	common
Pneumonitis	0.9	0.1	uncommon
Skin and Subcutaneous Tissue Disorders			
Pruritus	7.0	0	common
Rash	1.1	0	common
Vascular Disorders			
Haemorrhage	29.2	0.4*	very common
Hypertension	5.7	2.0	common

*Including one case of Grade 5 haemorrhage.

Laboratory Abnormalities

Table 5 displays laboratory abnormalities observed in patients treated with Kadcyla in clinical trial BO27938 (KATHERINE).

Table 5 Laboratory abnormalities from patients in Study BO27938 (KATHERINE)

Parameter	Kadcyla		
	All Grade %	Grade 3 %	Grade 4 %
Hepatic			
Increased Bilirubin	11	0	0
Increased AST	79	< 1	0
Increased ALT	55	< 1	0
Hematologic			
Decreased Platelets	51	4	2
Decreased Haemoglobin	31	1	0
Decreased Neutrophils	24	1	0

Potassium			
Decreased Potassium	26	2	< 1

Metastatic Breast Cancer

The safety of Kadcyla has been evaluated in more than 1,871 patients. Adverse drug reactions from clinical trials (**Table 6**) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 6 Adverse drug reactions occurring in patients treated with Kadcyla in clinical trials

System Organ Class	All grades (%) n = 1871	Grade 3 - 5 (%) n = 1871	Frequency Category
Blood and Lymphatic System Disorders			
Thrombocytopenia	24.9	8.7	very common
Anaemia	14.6	3.8	very common
Neutropenia	8.1	2.6	common
Cardiac Disorders			
Left ventricular dysfunction	2.2	0.4	common
Eye Disorders			
Dry eye	5.7	0.0	common
Lacrimation increased	4.1	0.0	common
Vision blurred	4.0	0.0	common
Conjunctivitis	3.8	0.0	common
Gastrointestinal Disorders			
Nausea	40.0	0.8	very common
Constipation	23.7	0.4	very common
Vomiting	19.9	1.0	very common
Diarrhoea	19.2	0.7	very common
Dry Mouth	16.0	< 0.1	very common
Abdominal pain	15.9	0.9	very common
Stomatitis	15.4	0.1	very common
Dyspepsia	8.0	0.1	common
General Disorders and Administration Site Conditions			
Fatigue	36.8	2.5	very common
Pyrexia	23.0	0.2	very common
Asthenia	16.3	1.1	very common

System Organ Class	All grades (%) n = 1871	Grade 3 - 5 (%) n = 1871	Frequency Category
Chills	10.3	≤ 0.1	very common
Oedema peripheral	8.1	0.1	common
Hepatobiliary Disorders			
Portal hypertension	0.3	0.1	uncommon
Hepatic failure	0.1	0.1	uncommon
Nodular regenerative hyperplasia	0.1	0.0	uncommon
Immune System Disorders			
Drug hypersensitivity	2.6	0.1	common
Infections and Infestations			
Urinary Tract Infection	11.9	0.4	very common
Injury, Poisoning, and Procedural Complications			
Infusion related reaction	4.0	0.3	common
Investigations			
Transaminases increased	24.2	7.2	very common
Blood alkaline phosphatase increased	5.3	0.5	common
Metabolism and Nutrition Disorders			
Hypokalaemia	11.0	2.4	very common
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal pain	35.5	2.4	very common
Arthralgia	18.9	0.6	very common
Myalgia	12.9	0.3	very common
Nervous System Disorders			
Headache	28.1	0.6	very common
Neuropathy peripheral	23.0	1.3	very common
Dizziness	9.5	0.2	common
Dysgeusia	6.4	0.0	common
Psychiatric Disorders			
Insomnia	11.7	0.2	very common
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	24.3	0.4	very common
Cough	19.5	0.1	very common
Dyspnoea	13.4	1.5	very common

System Organ Class	All grades (%) n = 1871	Grade 3 - 5 (%) n = 1871	Frequency Category
Pneumonitis	0.7	0.1	uncommon
Skin and Subcutaneous Tissue Disorders			
Rash	12.4	0.3	very common
Pruritus	6.0	≤ 0.1	common
Vascular Disorders			
Haemorrhage	34.8	2.2	very common
Hypertension	6.5	1.7	common

Laboratory Abnormalities
Table 7 displays laboratory abnormalities observed in patients treated with Kadcyla in Study TDM4370/BO21977 (EMILIA).

Table 7 Laboratory abnormalities in Study TDM4370g/BO21977 (EMILIA)

Parameter	Kadcyla		
	All Grade %	Grade 3 %	Grade 4 %
Hepatic			
Increased Bilirubin	21	< 1	0
Increased AST	98	8	< 1
Increased ALT	82	5	< 1
Haematologic			
Decreased Platelets	85	14	3
Decreased Haemoglobin	63	5	1
Decreased Neutrophils	41	4	< 1
Potassium			
Decreased Potassium	35	3	< 1

Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of Kadcyla or of other trastuzumab products.

A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to Kadcyla. Following Kadcyla dosing, 5.1% (64/1243) of patients tested positive for anti-Kadcyla 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-Kadcyla antibodies.

In the EMILIA study (TDM4370g/BO21977), 5.2% (24/466) of patients tested positive for anti-Kadcyla antibodies, of which 13 were also positive for neutralising antibodies. In the KATHERINE (BO27938) study, 4.0% (16/401) of patients tested positive for anti-Kadcyla antibodies, of which 5 of were also positive for neutralising antibodies. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of Kadcyla is unknown.

Post market setting

In the post marketing setting, very rare cases of epidermal injury or necrosis following extravasation have been observed within days to a few weeks after infusion (*see Section 4.4 Special Warnings and Precautions for Use*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for trastuzumab emtansine overdose. In case of overdose, the patient should be closely monitored. Cases of overdose have been reported with trastuzumab emtansine treatment, most associated with thrombocytopenia, and there was one death. In the fatal case, the patient incorrectly received trastuzumab emtansine 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to Kadcyla were not established.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre (in Australia call 13 11 26).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents, monoclonal

antibodies; ATC code: L01FD03

Mechanism of Action

Trastuzumab emtansine is a HER2-targeted antibody-drug conjugate, containing the humanised anti-HER2 IgG1 antibody trastuzumab, covalently linked to the small molecule cytotoxin, DM1. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalisation and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites.

Trastuzumab emtansine 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, trastuzumab emtansine, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits HER2 receptor signalling and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxic component of Kadcyla, binds to tubulin. By inhibiting tubulin polymerisation, both DM1 and Kadcyla cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death.

Clinical trials

Early Breast Cancer

BO27938 (KATHERINE)

KATHERINE was a randomised, multicentre, 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 enrolment. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumour samples were required to determine HER2 positive status defined as 3+ IHC or ISH amplification ratio ≥ 2.0 using a Pathway® HER2 (4B5) IHC assay and INFORM Dual ISH DNA Probe Cocktail (both Ventana) at a central laboratory. Patients were randomised (1:1) to receive trastuzumab or Kadcyla. Randomisation 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.

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 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).

Patient demographics and baseline tumour characteristics were balanced between treatment arms. The median age was approximately 49 years (range 23-80 years), 72.8% were White, 8.7% were Asian and 2.7% were Black or African American. All but 5 patients were women. 22.5 percent of patients were enrolled in North America, 54.2% in Europe and 23.3% throughout the rest of the world. Tumour prognostic characteristics including hormone receptor status (positive: 72.3%, negative: 27.7%), clinical stage at presentation (inoperable: 25.3%, operable: 74.8%) and pathological nodal status after preoperative therapy (node positive: 46.4%, node negative not evaluated: 53.6%) were similar in the study arms.

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen. 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.

At the time of primary analysis, a clinically meaningful and statistically significant improvement in IDFS was observed in patients who received Kadcyla 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 years IDFS rates were 88.3% vs. 77.0% in Kadcyla vs. trastuzumab arms, respectively. See **Table 8** and **Figure 1**.

The final descriptive IDFS analysis and second interim OS analysis, were conducted in the ITT population when 385 IDFS events had been observed. At that time, 215 OS events had been observed in the ITT population with a median duration of follow up of 101 months.

In the final descriptive IDFS analysis, Kadcyla reduced the risk of an IDFS event by 46% compared with trastuzumab (unstratified HR=0.54; 95% CI: 0.44–0.66). Estimates of IDFS event free rates at 7 years were 80.8% (95% CI: 77.86, 83.78) vs 67.1% (95% CI: 63.49, 70.65) in the Kadcyla and trastuzumab arms, respectively. IDFS results at the final descriptive IDFS analysis were consistent with the primary analysis.

The second interim OS analysis demonstrated a statistically significant and clinically meaningful improvement in OS for Kadcyla (34% reduction in risk of OS event; unstratified HR = 0.66, 95% CI: 0.51, 0.87, p=0.0027) compared with trastuzumab. A 4.7% improvement in 7 years OS rates was demonstrated in patients treated with Kadcyla (89.1%) compared to patients treated with trastuzumab (84.4%) (see **Table 8** and **Figure 2**).

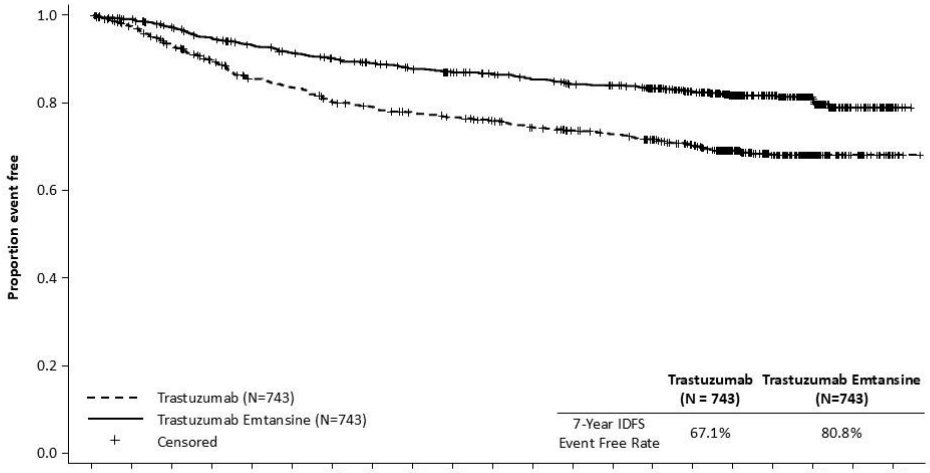
Table 8 Summary of Efficacy from KATHERINE

	Trastuzumab n = 743	**Kadcyla n = 743**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)[1]		
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[2], % [95% CI]	77.0 [73.78, 80.26]	88.3 [85.81, 90.72]
Secondary Endpoints[3]		
IDFS including second primary non-breast cancer[1,5]		
Number (%) of patients with event	167 (22.5%)	95 (12.8%)
HR [95% CI]	0.51 [0.40, 0.66]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2], % [95% CI]	76.9 [73.65, 80.14]	87.7 [85.18, 90.18]
Disease Free Survival (DFS) [1,5]		
Number (%) of patients with event	167 (22.5%)	98 (13.2%)
HR [95% CI]	0.53 [0.41, 0.68]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2], % [95% CI]	76.9 [73.65, 80.14]	87.4 [84.88, 89.93]
Overall Survival (OS)[3,4]		

	Trastuzumab n = 743	Kadcyla n = 743
Number (%) of patients with event	126 (17.0%)	89 (12.0%)
HR [95% CI]	0.66 [0.51, 0.87]	
p-value (Log-Rank test, unstratified)	0.0027	
7 year survival rate[2], % [95% CI]	84.4 [81.58, 87.16]	89.1 [86.71, 91.42]

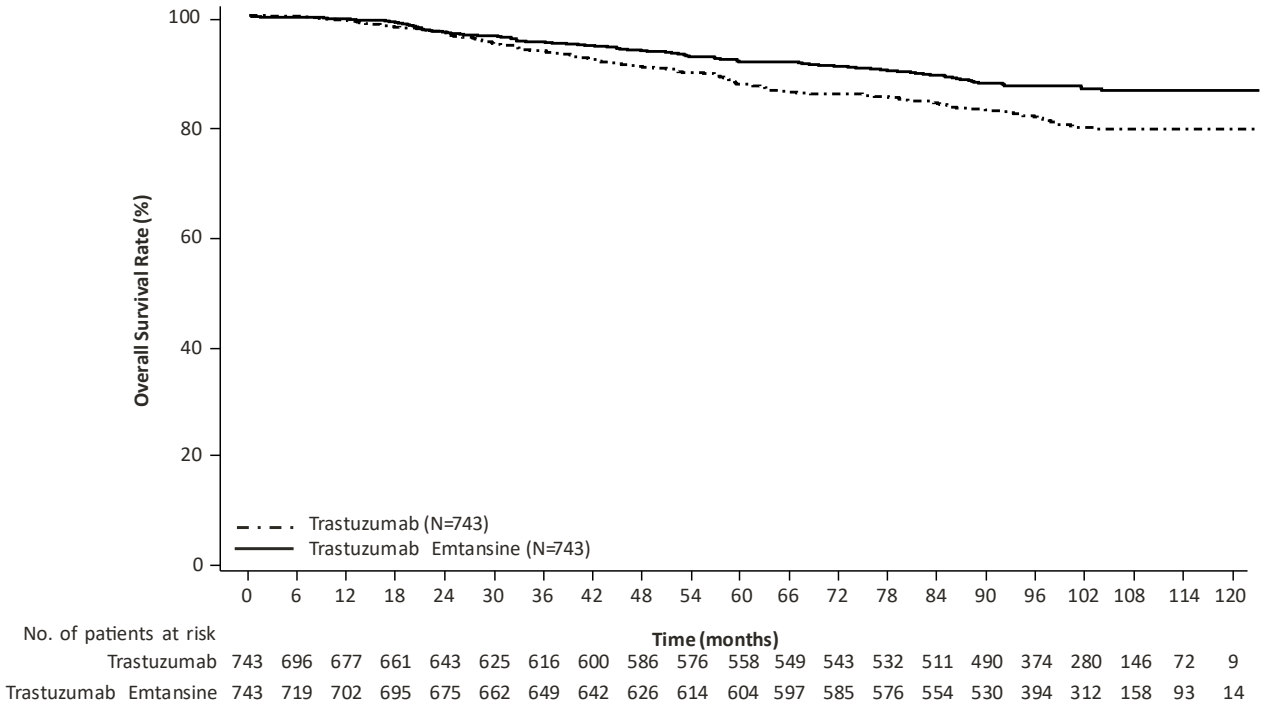
HR: Hazard Ratio; CI: Confidence Intervals,
[1] Data from primary analysis
[2] 3-year event-free rate and 7 year survival rate derived from Kaplan-Meier estimates
[3] Hierarchical testing applied for IDFS and OS
[4] Data from second interim OS analysis
[5] Endpoints not adjusted for multiplicity and not formally tested as per the hierarchical testing

Figure 1 Kaplan-Meier Curve of Invasive Disease-Free Survival in KATHERINE (updated analysis)



No. of patients at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
Patients with IDFS event	0	22	54	84	115	131	156	169	175	182	188	200	204	210	220	229	235	239	239	239	239
Patients censored	0	44	53	64	72	72	76	79	83	86	95	99	108	112	126	146	270	317	430	462	502
Trastuzumab Emtansine	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3
Patients with IDFS event	0	7	23	44	57	70	81	88	98	104	108	116	124	126	131	137	141	142	145	146	146
Patients censored	0	28	38	41	49	53	57	64	71	78	87	90	98	101	131	163	321	365	509	547	594

Figure 2 Updated Kaplan-Meier Curve of Overall Survival in KATHERINE



In KATHERINE, consistent treatment benefit of Kadcyla for IDFS was seen in all the pre-specified subgroups evaluated, supporting the robustness of the overall result.

Metastatic Breast Cancer

TDM4370g/BO21977 (EMILIA)

EMILIA is a phase III, randomised, multicentre, international, open-label clinical trial conducted in patients with HER2-positive unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer 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 enrolment, breast tumour samples were centrally confirmed to be HER2 positive, defined as a score of 3+ by IHC or gene amplification by ISH. Baseline patient and tumour characteristics were well balanced between treatment groups. For patients randomised to Kadcyla, the median age was 53 years, most patients were female (99.8%), the majority Caucasian (72%), and 57% had oestrogen-receptor and/or progesterone-receptor positive disease. The study compared the safety and efficacy of Kadcyla with that of lapatinib + capecitabine. A total of 991 patients were randomised with Kadcyla or lapatinib + capecitabine as follows:

- Kadcyla 3.6 mg/kg IV over 30 - 90 minutes on Day 1 of a 21-day cycle, or
- Lapatinib 1250 mg/day orally once per day of a 21-day cycle + capecitabine 1000 mg/m^2 orally twice daily on Days 1 - 14 of a 21-day cycle

The co-primary efficacy endpoints of the study were progression-free survival (PFS) as assessed by an independent review committee (IRC), overall survival (OS) and landmark (1-year and 2-year) survival rates.

Time to symptom progression, as defined by a 5-point decrease in score derived from the trial outcome index-breast (TOI-B) subscale of the Functional Assessment of Cancer Therapy-Breast Quality of Life (FACT-B QoL) questionnaire was also assessed during the clinical trial. A change of 5 points in the TOI-B is considered clinically significant.

Table 9 Summary of efficacy from TDM4370g/BO21977 (EMILIA) study

	Lapatinib + Capecitabine n = 496	**Kadcyla n = 495**
Primary Endpoints		
IRC-assessed PFS		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard Ratio (stratified [a])	0.650	
95% CI for Hazard Ratio	(0.549 , 0.771)	
p-value (Log-Rank test, stratified [a])	<0.0001	
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 [a])	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test [a])	0.0006	
Landmark 1 year survival rate	78.4%	85.2%
(95% CI)	(74.62, 82.26)	(81.99, 88.49)
Landmark 2 year survival rate	51.8%	64.7%
(95% CI)	(45.92, 57.73)	(59.31, 70.19)
Key Secondary Endpoints		
Investigator-assessed PFS		
Number (%) of patients with event	335 (67.5%)	287 (58.0%)
Median duration of PFS (months)	5.8	9.4
HR (95% CI)	0.658 (0.560, 0.774)	
p-value (Log-Rank test [a])	<0.0001	
Objective Response Rate		
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 [a])	0.0002	
Duration of Objective Response (months)		
Number of patients with OR	120	173
Median 95% CI	6.5 (5.5, 7.2)	12.6 (8.4, 20.8)
Time to Symptom Progression		
Number of evaluable patients	445	450
Number (%) of patients with event	257 (57.8%)	246 (54.7%)
Median time to event (months)	4.6	7.1
HR, 95% CI	0.796 (0.667, 0.951)	
p-value (Log-Rank test [a])	0.0121	

PFS: progression-free survival; OR: objective response

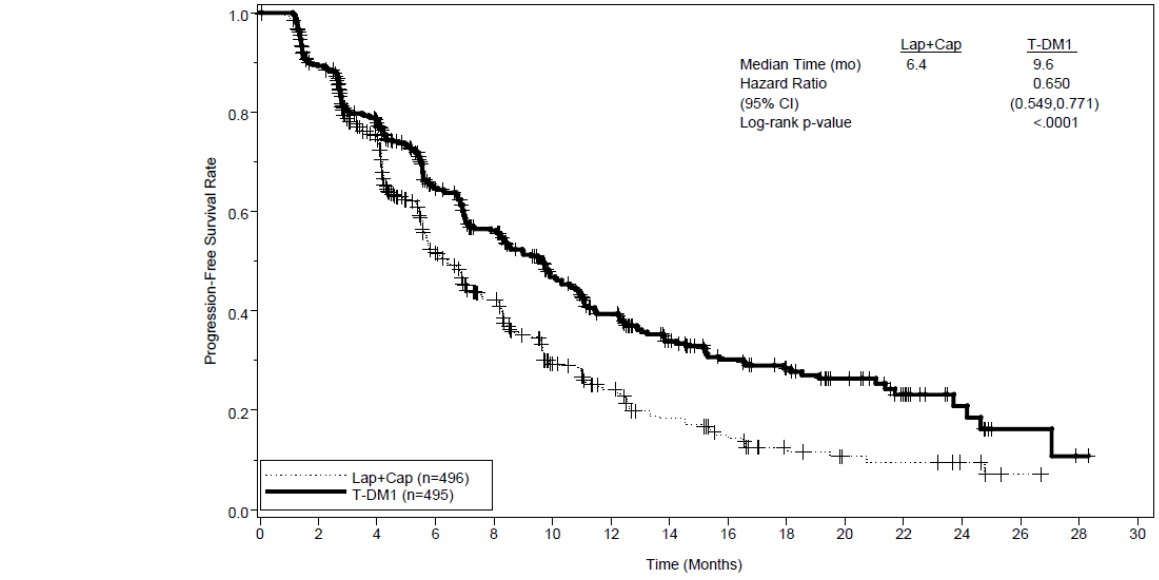
[a] Stratified by: world region (United States, Western Europe, Other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs. > 1), and visceral vs. non-visceral disease.

[b] 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 **Table 9**.

A treatment benefit was seen in the subgroup of patients who did not receive any prior systemic anti-cancer therapy in the metastatic setting (n=118); hazard ratio for PFS and OS were 0.51 (95% CI: 0.30, 0.85) and 0.61 (95% CI: 0.32, 1.16), respectively. The median PFS and OS for the Kadcyla group were 10.8 months and not reached, respectively, compared with 5.7 months and 27.9 months, respectively, for the lapatinib plus capecitabine group.

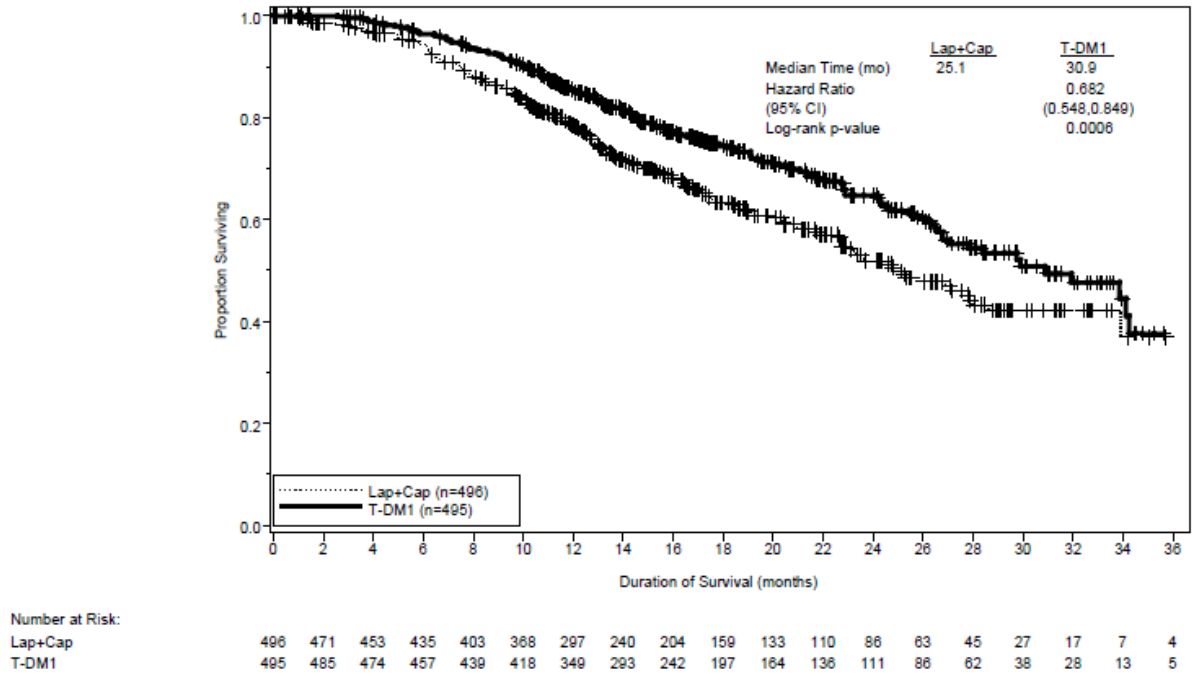
Of 495 patients who received Kadcyla in EMILIA, 65 patients (13%) were ≥ 65 years of age and 11 patients (2%) were ≥ 75 years of age. A trend for treatment benefit with Kadcyla compared to the control arm in terms of PFS for the subgroup of patients who were 65 to 74 years old was observed (total n=113; HR=0.88, 95% CI: 0.53, 1.45). For patients ≥ 75 years of age, based on IRC assessments, the hazard ratios for PFS and OS were 3.51 (95% CI: 1.22, 10.13) and 3.45 (95% CI: 0.94, 12.65), respectively. The subgroup of patients 75 years or above did not demonstrate a benefit for PFS or OS, but was too small (n=25) to draw any definitive conclusions.

Figure 3 Kaplan-Meier curve of IRC-assessed progression-free survival



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 4 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.

TDM4450g/BO21976
TDM4450g was a randomised, multicentre, open-label phase II study to evaluate the effects of Kadcyla versus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer who had not received prior chemotherapy for metastatic disease. Patients were randomised to receive Kadcyla, 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 + docetaxel 75-100 mg/m^2 IV every 3 weeks (n=70).

The primary endpoint was PFS assessed by the investigator. The median PFS was 9.2 months in the trastuzumab + docetaxel arm and 14.2 months in the Kadcyla arm (HR: 0.59; p=0.035), with a median follow-up of approximately 14 months in both arms. The ORR was 58.0% with trastuzumab + docetaxel and 64.2% with Kadcyla. The median duration of response was not reached with Kadcyla vs. median duration 9.5 months in the control arm.

The worsening of the FACT-B TOI scores was delayed in the Kadcyla arm compared with the control arm (median time to symptom progression was 7.5 months in the Kadcyla arm vs. 3.5 months in the control arm; HR: 0.58; p=0.022).

TDM4374g
TDM4374g was a phase II single-arm, open-label study to evaluate the effects of Kadcyla in patients with HER2 positive incurable, locally advanced, or metastatic breast cancer. 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 Kadcyla IV 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% (95% CI: 24.1, 42.1), n=36 responders, by both IRC and investigator review. The median duration of response by Independent Review Committee was not reached (95% CI, 4.6 months to not estimable).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Kadcyla is administered as an intravenous (IV) infusion. There have been no studies performed with other routes of administration.

Distribution

Kadcyla when administered IV every 3 weeks exhibited linear pharmacokinetics 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 the randomised pivotal trials, EMILIA and KATHERINE, who received 3.6 mg/kg of Kadcyla IV every 3 weeks, had a mean maximum serum concentration (Cmax) of trastuzumab emtansine in Cycle 1 of 83.4 (±16.5) μg/mL and 72.6 (± 24.3) μg/mL, respectively. Based on population pharmacokinetic analysis, following IV administration of Kadcyla, the central volume of distribution of trastuzumab emtansine was 3.13 L and approximated that of plasma volume.

In *in vitro* studies, DM1 was 93% bound to human plasma proteins and was shown to be a substrate of P-glycoprotein (P-gp).

Metabolism

Kadcyla 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 the randomised trials EMILIA and KATHERINE, mean maximum DM1 levels in Cycle 1 following Kadcyla administration were consistently low and averaged 4.61 (± 1.61) ng/mL and 4.71 (± 2.25) ng/mL, respectively.

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

Excretion

Based on population pharmacokinetic analysis, following IV administration of Kadcyla, the clearance of trastuzumab emtansine was 0.68 L/day and the elimination half-life ($t_{1/2}$) was approximately 4 days. No accumulation of trastuzumab emtansine was observed after repeated dosing of Kadcyla IV infusions every 3 weeks.

Based on population pharmacokinetic analysis (n=671), body weight, albumin, sum of longest diameter of target lesions by Response Evaluation Criteria in Solid Tumours (RECIST), HER2 shed ECD, baseline trastuzumab concentrations, and AST were identified as statistically significant covariates for trastuzumab emtansine pharmacokinetic parameters. However, the magnitude of effect of these covariates on trastuzumab emtansine exposure, suggests that, with the exception of body weight, these covariates are unlikely to have any clinically meaningful effect on Kadcyla exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates is considered appropriate.

In rats, trastuzumab emtansine catabolites, including DM1, Lys-MCC-DM1, and MCC-DM1 were shown to be mainly excreted in the bile with minimal elimination in urine.

Pharmacokinetics in special populations

The population pharmacokinetic analysis of trastuzumab emtansine showed that race did not appear to influence the pharmacokinetics of Kadcyla. Pharmacokinetics of Kadcyla in Asian patients (n=73) were similar to non-Asian patients (n=598). Because most of the patients in Kadcyla clinical studies were females, effect of gender on the pharmacokinetics of Kadcyla was not formally evaluated.

Elderly

The population pharmacokinetic analysis of trastuzumab emtansine showed that age did not affect the pharmacokinetics of Kadcyla. No significant difference was observed in the pharmacokinetics of trastuzumab emtansine among patients <65 years (n=577), patients between 65-75 years (n=78) and patients >75 years (n=16).

Renal Impairment

The population pharmacokinetic analysis of trastuzumab emtansine showed that creatinine clearance (CLcr) does not affect pharmacokinetics of Kadcyla. Pharmacokinetics of trastuzumab emtansine in patients with mild (CLcr 60-89 mL/min, n=254) or moderate (CLcr 30 to 59 mL/min, n=53) renal impairment were similar to those in patients with normal renal function (CLcr ≥90 mL/min, n=361). Pharmacokinetic data in patients with severe renal impairment (CLcr 15-29 mL/min) is limited (n=1), therefore no dosage recommendations can be made.

Hepatic Impairment

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 Kadcyla 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 MCC-DM1 were low and comparable between patients with and without hepatic impairment. Plasma concentrations of Lys-MCC-DM1 were minimal in subjects with and without hepatic impairment.
- 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 than in patients with normal hepatic function. There are insufficient data to characterise 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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A limited monkey micronucleus assay did not identify any clastogenic potential for trastuzumab emtansine. While DM1 did not demonstrate any mutagenic potential in the bacterial reverse mutation (Ames test) *in vitro*, it was shown to be dose-dependently clastogenic in the rat micronucleus assay *in vivo* at anticipated therapeutic DM1 exposure levels.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Succinic acid
Sodium hydroxide
Sucrose
Polysorbate 20

6.2 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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage conditions

Store vials in a refrigerator at 2-8°C. Do not use after the expiry date (EXP) shown on the pack.

Shelf-life of reconstituted solution

Kadcyla vials reconstituted with Sterile Water for Injection (SWFI) 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 solution for infusion containing the reconstituted product

The reconstituted Kadcyla 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. Particulates may be observed on storage if diluted in 0.9% Sodium Chloride Injection, therefore, a 0.22 micron in-line polyethersulfone (PES) filter is required for administration *(see Section 4.2 Dose and method of administration)*.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Available in single-use glass vials containing 100 mg or 160 mg of Kadcyla powder for concentrate solution, designed to deliver 5 mL or 8 mL respectively, of 20 mg/mL trastuzumab emtansine.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions for reconstitution

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

The reconstituted product does not contain preservative and is for single use in one patient only. Discard any residue.

- Using a sterile syringe, slowly inject 5 mL of SWFI into the 100 mg vial, or 8 mL of SWFI into the 160 mg vial.
- Swirl the vial gently until completely dissolved. DO NOT SHAKE!

Reconstituted solution should be inspected visually for particulate matter and discolouration 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 use if the reconstituted solution contains visible particulates, is cloudy or discoloured.

Instructions for dilution

Determine the volume of solution required based on a dose of 3.6 mg Kadcyla / kg body weight (*see section 4.2 Dose and method of administration; Dose Adjustment*):

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg})}{\textbf{20}\ \text{mg/mL (conc. of reconstituted solution)}}$$

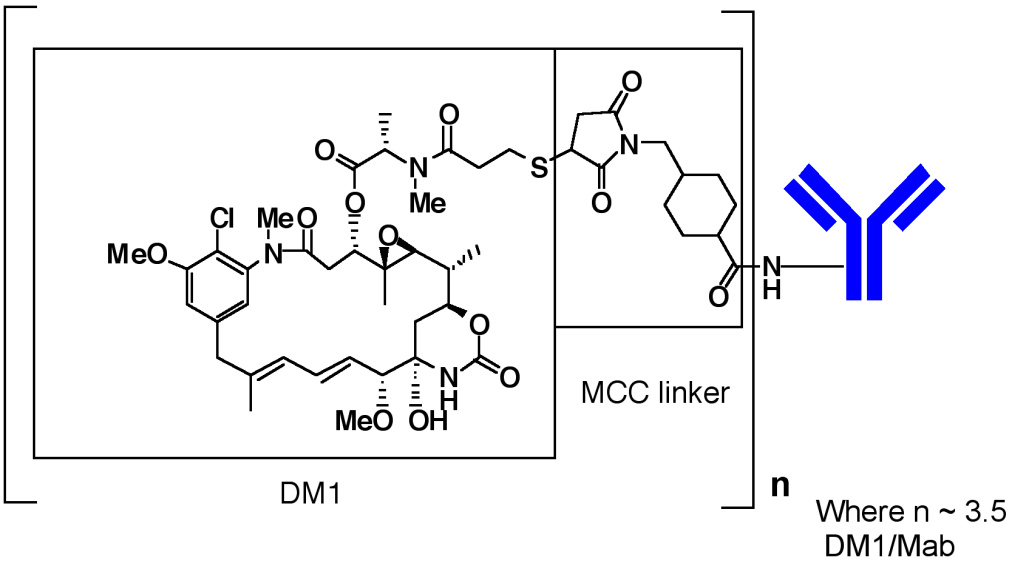
The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.45% sodium chloride or 0.9% sodium chloride. Dextrose (5%) solution should not be used.

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Note: The bracketed structure is DM1 plus MCC which represents the emtansine component. The n is, on average, 3.5 DM1 molecules per trastuzumab (Mab) molecule.

Kadcyla (trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate that contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) with the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. The antibody trastuzumab, is a well characterised recombinant monoclonal antibody product produced by mammalian (Chinese hamster ovary) cells, and the small molecule components (DM1 and MCC) are produced by chemical synthesis. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.

CAS number
1018448-65-1

7. MEDICINE SCHEDULE (POISONS STANDARD)
Schedule 4 – Prescription Only Medicine

8. SPONSOR
Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA
Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL
03 September 2013

10. DATE OF REVISION

25 March 2026

Summary table of changes

Section Changed	Summary of new information
4.8 and 5.1	Update of adverse effects and clinical trial information following finalisation of the KATHERINE clinical trial
4.9 and 8	Deletion of NZ-specific information
5.1	Update of ATC code