SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Kadcyla® 100, powder for concentrate for solution for infusion

Kadcyla® 160, powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Kadcyla contains trastuzumab emtansine as the active substance.

Kadcyla 100 mg powder for concentrate for solution for infusion

One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab emtansine. After reconstitution one vial of 5 mL solution contains 20 mg/mL of trastuzumab emtansine (see section 6.6).

Kadcyla 160 mg powder for concentrate for solution for infusion

One vial of powder for concentrate for solution for infusion contains 160 mg of trastuzumab emtansine. After reconstitution one vial of 8 mL solution contains 20 mg/mL of trastuzumab emtansine (see section 6.6).

Contains sugar (sucrose).

For a full list of the excipients, see section 6.1

Trastuzumab emtansine is an antibody-drug conjugate that contains trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture, covalently linked to DM1, a microtubule inhibitor, via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Breast cancer:

Early Breast Cancer (EBC)

Kadcyla is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease, after pre-operative systemic treatment.

Metastatic Breast Cancer (MBC)

Kadcyla is indicated as monotherapy for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

4.2 Posology and method of administration

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

Kadcyla therapy should only be administered as an intravenous infusion under the supervision of a healthcare professional experienced in the treatment of cancer patients (prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available (see section 4.4).

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) or by fluorescence in situ hybridization (FISH) assessed by a validated test.

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Substitution by any other biological medicinal product requires the consent of the prescribing medical practitioner.

Kadcyla must be reconstituted and diluted by a healthcare professional and administrated as an intravenous infusion (see section 6.6). Do not administer as an intravenous push or bolus.

Posology

The recommended dose of Kadcyla is 3,6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle)

Administer the initial dose 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 administration (see section 4.8).

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 sections 4.4 and 4.8). Discontinue Kadcyla for life-threatening infusion reactions.

***Duration of treatment*:**

Early breast cancer (EBC)

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

Metastatic breast cancer (MBC)

Patients with MBC should receive treatment until disease progression or unmanageable toxicity.

Dose modification

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

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

Dose modifications for patients with EBC		
Adverse reaction	**Severity**	**Treatment modification**
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.
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
Hyperbilirubinaemia	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
Drug Induced Liver Injury (DILI)	Serum transaminases >3× ULN and	Permanently discontinue Kadcyla in the absence of

	concomitant total bilirubin >2× ULN	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 Kadcyla
Peripheral Neuropathy	Grade 3-4	Do not administer Kadcyla until resolution ≤ Grade 2
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
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

Dose modifications for patents with MBC		
Adverse reaction	**Severity**	**Treatment modification**
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
Increased Transaminase (AST/ALT)	Grade 2 (> 2,5 to ≤ 5× the ULN) ~~on day of~~	Treat at the same dose level

	~~scheduled treatment)~~	
	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
Hyperbilirubinaemia	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 x 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
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue Kadcyla
Left Ventricular Dysfunction	Symptomatic CHF	Discontinue Kadcyla
	LVEF <40 %	Do not administer Kadcyla 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.
Pulmonary Toxicity	Interstitial lung disease (ILD or pneumonitis)	Permanently discontinue Kadcyla
Peripheral Neuropathy	Grade 3 - 4	Do not administer Kadcyla until resolution to Grade ≤ 2

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 Kadcyla treatment.

Delayed or missed dose:

If a planned dose 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 next dose should be administered in accordance with dosing recommendations above.

Peripheral neuropathy

Kadcyla should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. At retreatment a dose reduction may be considered according to the dose reduction schedule (see Table 1).

Special Populations

Elderly patients

No dose adjustment of Kadcyla is required in patients aged ≥ 65 years.

Renal Impairment

No adjustment to the starting dose of Kadcyla is needed in patients with mild or moderate renal impairment (see section 5.2). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data and therefore patients with severe renal impairment should be monitored carefully.

Hepatic Impairment

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment (see section 5.2). 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 sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Kadcyla in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of breast cancer.

Method of administration

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

For instructions on reconstitution and dilution of Kadcyla before administration, see section 6.6.

4.3 Contraindications

Kadcyla is contraindicated in patients with a known hypersensitivity to trastuzumab emtansine or any of the excipients of Kadcyla (see section 6.1).

Pregnancy and Lactation (see section 4.6).

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.

Immunogenicity

A total of 1 243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to Kadcyla. Following Kadcyla dosing, 5,1 % (63/1 243) of patients tested positive for anti-trastuzumab emtansine 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-trastuzumab emtansine antibodies. In the MBC study, 5,2 % (24/466) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 13 were also positive for neutralising antibodies. In the EBC study, 3,7 % (15/401) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 5 of were also positive for neutralising antibodies. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti-trastuzumab emtansine antibodies on the pharmacokinetics, safety, and efficacy of Kadcyla.

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 studies with Kadcyla (see section 4.8). 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).

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

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), has been observed while on treatment with Kadcyla in clinical trials (see section 4.8). 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 (the proportion of patients with Grade 1-2 ALT/AST abnormalities increases with successive cycles).

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. Observed cases have been confounded by comorbidities and/or concomitant medicines with known hepatotoxic potential.

Liver function should be monitored prior to initiation of treatment and each Kadcyla dose. Patients with baseline elevation of ALT (e.g. due to liver metastasis) may be predisposed to liver injury with a higher risk of a Grade 3-5 hepatic event or liver function test increase. Dose reductions or discontinuation for increased serum transaminases and total bilirubin are specified in section 4.2.

Kadcyla has not been studied in patients with serum transaminases > 2,5 x ULN or total bilirubin > 1,5 x ULN prior to initiation of treatment. Kadcyla treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN should be permanently discontinued.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with Kadcyla. NRH is a 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. Treatment of patients with hepatic impairment should be undertaken with caution (see sections 4.2 and 5.2).

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 commonly in patients treated with Kadcyla, and therefore symptomatic congestive heart failure (CHF) is a potential risk.

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.

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.

The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see section 4.2).

Infusion-Related Reactions (IRR)

Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to IRR; treatment with Kadcyla is not recommended for these patients. Patients should be observed carefully for infusion-related reactions, especially during the first infusion.

IRR, characterised by one or more of the following symptoms - flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia have been reported. 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 until signs and symptoms resolve. Consideration for re-treatment should be based on clinical assessment of the severity of the reaction. Kadcyla treatment must be permanently discontinued in the event of a life threatening IRR (see section 4.2).

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity/allergic reactions, Serious anaphylactic reactions, have been observed in clinical trials with Kadcyla. Medicines to treat such reactions, as well as emergency equipment, should be available for immediate use. In the event of a true hypersensitivity reaction (in which the severity of the reaction increases with subsequent infusions), Kadcyla treatment must be permanently discontinued.

Haemorrhage

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

Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was commonly reported with Kadcyla and was the most common adverse reaction leading to treatment discontinuation, dose reduction, and dose interruption (see section 4.8). In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

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 < 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 (≥ 75 000/mm^3) (see section 4.2).

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.

Extravasation

In Kadcyla clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild or moderate 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. Specific treatment for Kadcyla extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during administration.

Sucrose

Kadcyla contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Contains sucrose: Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Kadcyla.

Sodium content in excipients

Kadcyla contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium free”.

4.5 Interaction with other medicines and other forms of interaction

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

In vitro metabolism studies in human liver microsomes suggest that DM1, a component of Kadcyla, is metabolised mainly by CYP3A4 and, to a lesser extent, by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazadone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) with Kadcyla should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medicine with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying Kadcyla 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 inhhibitor is coadministered and Kadcyla treatment cannot be delayed, patients should be closely monitored for adverse reactions.

4.6 Fertility, pregnancy and lactation

Safety and efficacy has not been established.

Contraception:

Women of childbearing potential should use effective contraception during treatment with Kadcyla and for at least 7 months following the last dose of Kadcyla. Male patients of their female partners should also receive effective contraception.

Pregnancy

Kadcyla is contraindicated in pregnancy and lactation (see section 4.3).

There are no data from the use of Kadcyla in pregnant women.

Trastuzumab, a component of Kadcyla, can cause foetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule inhibiting cytotoxic drug component of Kadcyla, is expected to be teratogenic and potentially embryotoxic.

Administration of Kadcyla to pregnant women is not recommended. 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 Kadcyla, close monitoring by a multidisciplinary team is recommended.

Breastfeeding

It is not known whether Kadcyla is excreted in human milk. Women should discontinue breastfeeding prior to initiating treatment with Kadcyla. Women may begin breastfeeding 7 months following the last dose of Kadcyla.

Fertility

No reproductive and developmental toxicology studies have been conducted with Kadcyla.

4.7 Effects on ability to drive and use machines

Kadcyla can cause adverse reactions such as fatigue, headache, dizziness and blurred vision which may impair the ability to drive or use machines. Patients experiencing infusion-related reactions (flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heart-beat) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of Kadcyla has been evaluated in 2 611 breast cancer patients in clinical studies. In this patient population:

- the most common serious ADRs (> 0,5 % of patients) were haemorrhage, pyrexia, dyspnoea, musculoskeletal pain, thrombocytopenia, abdominal pain and vomiting.
- the most common adverse drug reactions (ADRs) (≥ 25 %) with Kadcyla were nausea, fatigue, headache, musculoskeletal pain, peripheral neuropathy, thrombocytopenia, haemorrhage and increased transaminases. The majority of ADRs reported were of Grade 1 or 2 severity.

- the most common National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3 ADRs (> 2 %) were thrombocytopenia, increased transaminases, anaemia, neutropenia, fatigue, hypokalaemia, musculoskeletal pain and haemorrhage.

a) Tabulated list of adverse reactions

The ADRs in 2 611 patients treated with Kadcyla are presented in Table 3. The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency.

In this section, the following categories of frequency have been used: 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) and not known (cannot be estimated from the available data).

Within each frequency grouping and SOC, adverse reactions are presented in order of decreasing seriousness. ADRs were reported using NCI-CTCAE for assessment of toxicity.

Table 3 Summary of ADR's in patients treated with Kadcyla in clinical trials

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia	Neutropenia Leucopenia	
Immune system disorders		Drug hypersensitivity	
Metabolism and nutrition disorders		Hypokalaemia	
Psychiatric disorders	Insomnia		
Nervous system disorders	Peripheral neuropathy, Headache	Dizziness, Dysgeusia, Memory impairment	

Eye disorders		Dry eye, Conjunctivitis, Blurred vision, Increased lacrimation	
Cardiac disorders		Left ventricular dysfunction	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Epistaxis, Cough, Dyspnoea		Pneumonitis (ILD)
Gastrointestinal disorders	Stomatitis, Diarrhoea, Vomiting, Nausea, Constipation, Dry mouth, Abdominal pain	Dyspepsia, Gingival bleeding	
Hepatobiliary disorders	Increased transaminases	Increased blood alkaline phosphatase, Increased blood bilirubin	Hepatotoxicity, Hepatic failure, Nodular regenerative hyperplasia, Portal hypertension
Skin and subcutaneous disorders		Rash, Pruritis, Alopecia, Nail disorder, Palmar-plantar erythrodysaethesia syndrome, Urticaria	
Musculoskeletal and	Musculoskeletal pain,		

connective tissue disorders	Arthralgia, Myalgia		
General disorders and administration site conditions	Fatigue, Pyrxia, Asthenia	Peripheral oedema, Chills	Injection site extravasation
Injury, poisoning and procedural complications		Infusion-related reactions, radiation pneumonitis	

Table 3 shows pooled data from the overall treatment period in the MBC studies (N=1 871; median number of cycles of Kadcyla was 10) and in EBC studies (N=740; median number of cycles was 14).

c. Description of selected adverse reactions from clinical trials

Thrombocytopenia

Thrombocytopenia or decreased platelet counts were reported in 24,9 % of patients in MBC clinical studies with Kadcyla and was the most common adverse reaction leading to treatment discontinuation (2,6 %). Thrombocytopenia was reported in 28,5 % of patients in EBC clinical studies with Kadcyla and was the most common reported adverse reaction for all grades and ≥3, as well as the most common adverse reaction leading to discontinuation (4,2 %), dose interruptions, and dose reductions. The majority of the patients had Grade 1 or 2 events (≥ 50 000/mm^3), with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥ 75 000/mm^3) by the next scheduled dose. In clinical studies, the incidence and severity of thrombocytopenia were higher in Asian patients. Independent of race, the incidence of Grade 3 or 4 events (< 50 000/mm^3) was 8,7 % in patients with MBC treated with Kadcyla and 18,8 % in patients with EBC. For dose modifications for thrombocytopenia, see sections 4.2 and 4.4.

Haemorrhage

Haemorrhagic events were reported in 34,8 % of patients in MBC clinical trials with Kadcyla and the incidence of severe haemorrhagic events (Grade ≥3) occurred in 2,2 %. Haemorrhagic events were

reported in 29 % of patients with EBC and the incidence of severe haemorrhagic events (Grade ≥3) was 0,4 %, including one Grade 5 event. In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors. Cases of bleeding events with a fatal outcome have been observed in both MBC and EBC.

Increased transaminases (AST/ALT)

Increase in serum transaminases (Grade 1-4) has been observed during treatment with Kadcyla in clinical studies (see section 4.4). Transaminase elevations were generally transient. A cumulative effect of Kadcyla on transaminases has been observed, and generally recovered when treatment was discontinued. Increased transaminases were reported in 24,2 % of patients in MBC clinical studies. Grade 3 or 4 increased AST and ALT were reported in 4,2 % and 2,7 % of patients with MBC respectively and usually occurred in the early treatment cycles (1-6). Increased transaminases were reported in 32,4 % of patients with EBC. Grade 3 and 4 increased transaminases were reported in 1,5 % of patients with EBC. In general, the Grade ≥ 3 hepatic events were not associated with poor clinical outcome; subsequent follow-up values tended to show improvement to ranges allowing the patient to remain on study and continue to receive study treatment at the same or reduced dose. No relationship was observed between Kadcyla exposure (AUC), Kadcyla maximum serum concentration (C_{max}), total trastuzumab exposure (AUC), or C_{max} of DM1 and increases in transaminase. For dose modifications in the event of increased transaminases, see sections 4.2 and 4.4.

Left ventricular dysfunction

Left ventricular dysfunction was reported in 2,2 % of patients in clinical studies with Kadcyla. The majority of events were asymptomatic Grade 1 or 2 decrease in LVEF. Grade 3 or 4 events were reported in 0,4 % of patients with MBC. In the EBC study, left ventricular dysfunction was reported in 3,0 % of patients, with Grade 3 or 4 in 0,5 % of patients. Additional LVEF monitoring is recommended for patients with LVEF ≤ 45 % (See Table 5 in section 4.2 for specific dose modifications).

Peripheral neuropathy

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of Kadcyla. In patients with MBC, the overall incidence of peripheral neuropathy was 29,0 % and 8,6 % for Grade ≥ 2. In patients with EBC, the overall incidence was 32,3 % and 10,3 % for Grade ≥ 2.

Infusion-related reactions

Infusion-related reactions are characterised by one or more of the following symptoms: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia. Infusion-related reactions were reported in 4,0 % of patients in MBC clinical studies with Kadcyla, with six Grade 3 and no Grade 4 events reported. Infusion-related reactions were reported in 1,6 % of patients with EBC, with no Grade 3 or 4 events reported. Infusion-related reactions resolved over the course of several hours to a day after the infusion was terminated. No dose relationship was observed in clinical studies. For dose modifications in the event of infusion-related reactions, see sections 4.2 and 4.4.

Hypersensitivity reactions

Hypersensitivity was reported in 2,6 % of patients in MBC clinical studies with Kadcyla, with one Grade 3 and one Grade 4 events reported. Hypersensitivity was reported in 2,7 % of patients with EBC, with Grade 3 or 4 in 0,4 % of patients. Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. For dose modifications in the event of hypersensitivity reactions, see sections 4.2 and 4.4.

Laboratory abnormalities

Tables 4 and 5 displays laboratory abnormalities observed in patients treated with Kadcyla in the metastatic and early breast cancer clinical studies.

Table 4 Laboratory abnormalities observed in patients treated with Kadcyla in the Metastatic Breast Cancer studies

Parameter	**Trastuzumab emtansine (N=490)**		
	All Grades (%)	**Grade 3 (%)**	**Grade 4 (%)**
Hepatic			
Increased bilirubin	21	< 1	0
Increased AST	98	8	< 1
Increased ALT	82	5	< 1
Haematologic			
Decreased platelet count	85	14	3
Decreased haemoglobin	63	5	1
Decreased neutrophils	41	4	< 1
Potassium			
Decreased potassium	35	3	< 1

Table 5 Laboratory abnormalities observed in patients treated with Kadcyla in the Early Breast Cancer study

Parameter	**Trastuzumab emtansine (N=740)**		
	All Grades (%)	**Grade 3 (%)**	**Grade 4 (%)**
Hepatic			
Increased bilirubin	11	0	0

Increased AST	79	< 1	0
Increased ALT	55	< 1	0
Haematologic			
Decreased platelet count	51	4	2
Decreased haemoglobin	31	1	0
Decreased neutrophils	24	1	0
Potassium			
Decreased potassium	26	2	< 1

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no known antidote for trastuzumab emtansine overdose. In case of overdose, the patient should be closely monitored for signs and symptoms of adverse reactions and appropriate symptomatic treatment instituted. Cases of overdose have been reported with Kadcyla 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 was not established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, monoclonal antibodies; ATC code: L01XC14.

Mechanism of action

Trastuzumab emtansine is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (amaytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex.

Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalisation and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

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 signalling 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 component of trastuzumab emtansine, binds to tubulin. By inhibiting tubulin polymerisation, DM1 causes cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death.

Clinical efficacy

Early Breast Cancer

BO27938 (KATHERINE) was a randomised, multicenter, open-label trial of 1 486 patients with HER2-positive, early breast cancer with residual invasive tumor (patients who had not received pathological complete response (pCR)) in the breast and/or axillary lymph nodes following completion of preoperative systemic therapy that included chemotherapy and HER-2 targeted therapy. 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 ≥ 2.0 determined at a central laboratory. Patients were randomised (1:1) to receive trastuzumab or trastuzumab emtansine. Randomisation was stratified by clinical stage at presentation (operable vs inoperable), hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluated after preoperative therapy.

Trastuzumab emtansine 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 trastuzumab emtansine or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity, whichever occurred first. Patients who discontinued trastuzumab emtansine 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 randomisation 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. 3 men were included in the trastuzumab arm and 2 in the trastuzumab emtansine arm. 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. 93,8 % of these patients received pertuzumab. All of the patients had received taxanes as part of neoadjuvant chemotherapy.

A clinically meaningful and statistically significant improvement in IDFS was observed in patients who received trastuzumab emtansine compared with trastuzumab (HR = 0,50, 95 % CI [0,39, 0,64], p <0,0001). Estimates of 3 years IDFS rates were 88,3 % vs. 77,0 % in trastuzumab emtansine vs. trastuzumab arms, respectively. See Table 6 and Figure 1.

Table 6 Summary of Efficacy from BO27938 (KATHERINE) study

	Trastuzumab **N= 743**	**Trastuzumab Emtansine** **N= 743**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)[3]		

	Trastuzumab **N= 743**	**Trastuzumab Emtansine** **N= 743**
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[1]		
Overall Survival (OS)[3] Number (%) of patients with event	56 (7,5 %)	42 (5,7 %)
HR [95 % CI]	0,70 [0,47, 1,05]	
p-value (Log-Rank test, unstratified)	0,0848	
5 year survival rate[2], % [95 % CI]	86,8 [80,95, 92,63]	92,1 [89,44, 94,74]
IDFS including second primary non-breast cancer[3] 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) [3] 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]
Distant recurrence-free interval (DRFI)[3] Number (%) of patients with event	121 (16,3 %)	78 (10,5 %)

	Trastuzumab **N= 743**	**Trastuzumab** **Emtansine** **N= 743**
HR [95 % CI]	0,60 [0,45, 0,79]	
p-value (Log-Rank test, unstratified)	0,0003	
3 year event-free rate[2], % [95 % CI]	83,0 [80,10, 85,92]	89,7 [87,37, 92,01]

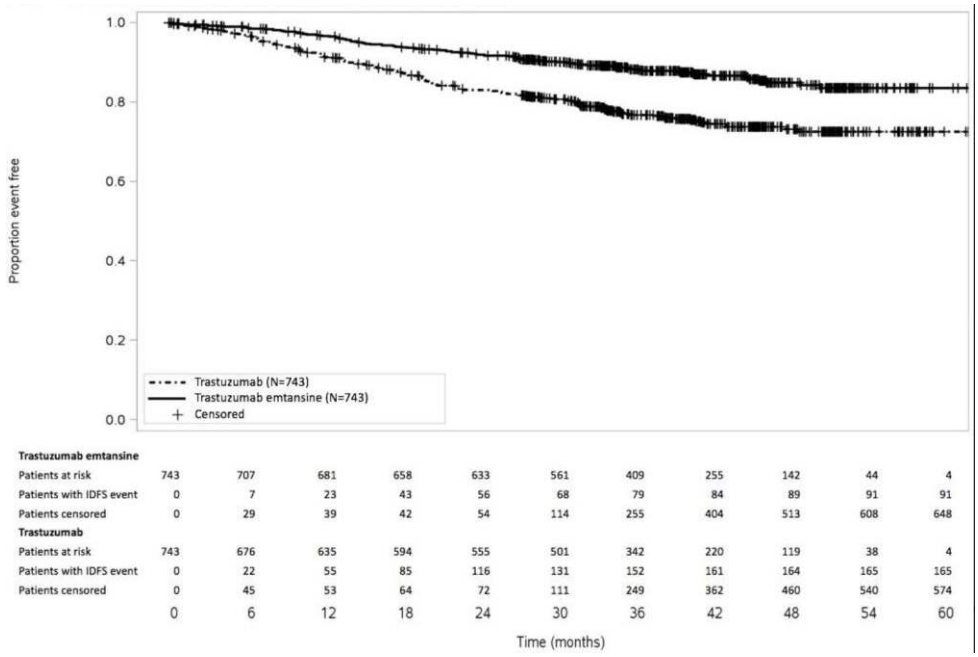
Key to abbreviations (Table 6): HR: Hazard Ratio; CI: Confidence Intervals,

1. Hierarchical testing applied for IDFS and OS

2. 3-year event-free rate and 5 year survival rate derived from Kaplan-Meier estimates

3. These secondary endpoints were not adjusted for multiplicity

Figure 1 Kaplan-Meier Curve of Invasive Disease Free Survival in KATHERINE



Trastuzumab emtansine											
Patients at risk	743	707	681	658	633	561	409	255	142	44	4
Patients with IDFS event	0	7	23	43	56	68	79	84	89	91	91
Patients censored	0	29	39	42	54	114	255	404	513	608	648
Trastuzumab											
Patients at risk	743	676	635	594	555	501	342	220	119	38	4
Patients with IDFS event	0	22	55	85	116	131	152	161	164	165	165
Patients censored	0	45	53	64	72	111	249	362	460	540	574
	0	6	12	18	24	30	36	42	48	54	60

Time (months)

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

5.2 Pharmacokinetic properties

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

Distribution

Trastuzumab emtansine when administered intravenously every 3 weeks exhibited linear pharmacokinetics across doses ranging from 2,4 to 4,8 mg/kg.

Patients in Study TDM4370g/BO21977 and Study BO29738 who received 3,6 mg/kg of trastuzumab emtansine intravenously every 3 weeks had a mean maximum serum concentration (C_{max}) of trastuzumab emtansine of 83,4 (± 16,5) μg/mL and 72,6 (± 24,3) μg/mL, respectively. Based on population pharmacokinetic analysis, following intravenous administration, the central volume of distribution of trastuzumab emtansine was (3,13 L) and approximated that of plasma volume.

Biotransformation (trastuzumab emtansine and DM1)

Trastuzumab emtansine is expected to undergo catabolism by means of proteolysis in cellular lysosomes. Catabolites including Lys-MCC-DM1, MCC-DM1 and DM1 are detected at low levels in human plasma. In study TDM4370g/BO21977 and Study BO29738, mean maximum DM1 levels in Cycle 1 following trastuzumab emtansine 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.

Elimination

Based on population pharmacokinetic (PK) analysis, following IV administration of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer, 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 IV infusion every 3 weeks.

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.

Pharmacokinetics in Special Populations

Elderly patients

The population pharmacokinetic analysis of trastuzumab emtansine showed that age did not affect the pharmacokinetics of trastuzumab emtansine. 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 does not affect pharmacokinetics of trastuzumab emtansine. Pharmacokinetics of trastuzumab

emtansine in patients with mild (creatinine clearance CLcr 60-89 mL/min, n=254) or moderate (CLcr 30-59 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 trastuzumab emtansine 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 comparable between patients 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 or moderate hepatic dysfunction was within the range observed in patients with normal hepatic function.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20

Sodium hydroxide

Succinic acid

Sucrose

6.2 Incompatibilities

Glucose (5 %) solution should not be used for reconstitution or dilution since it causes aggregation of the protein.

Kadcyla must not be mixed or diluted with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

36 months.

Reconstituted solution

Kadcyla 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.

Diluted solution:

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 0,2 or 0,22 micron in-line polyethersulfone (PES) filter is required for administration (see section 6.6*)*.

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

6.4 Special precautions for storage

Store vials in a refrigerator between 2 - 8 °C.

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

For storage conditions after reconstitution and dilution of Kadcyla, see section 6.3

6.5 Nature and contents of container

Kadcyla 100: Pack of 1 vial. Colourless 15 mL Type 1 glass vial closed with a fluoro-resin laminated grey butyl rubber stopper, sealed with an aluminium seal and a white plastic flip-off cap.

Kadcyla 160: Pack of 1 vial. Colourless 20 mL Type 1 glass vial closed with a fluoro-resin laminated grey butyl rubber stopper, sealed with an aluminium seal and a purple plastic flip-off cap.

6.6 Special precautions for disposal and other handling

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

Instructions for reconstitution

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

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

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 reconstituted solution contains visible particulates, or is cloudy, or is discoloured.

Instructions for dilution

Determine the volume of the solution required based on a dose of 3,6 mg Kadcyla/kg body weight *(*see section 4.2, Table 1 for *Dose reduction schedule)*:

Volume (mL) = **Body weight** (kg) x **dose** (mg/kg)

20 mg/mL (concentration 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. Glucose (5 %) solution should not be used (see section 6.2). 0,45 % sodium chloride may be used without a 0,2 or 0,22 micron in-line polyethersulfone (PES) filter. If 0,9 % sodium chloride is used for infusion, a 0,2 or 0,22 micron in-line 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. Do not freeze or shake the infusion during storage.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Kadcyla 100: 49/32.16/0197

Kadcyla 160: 49/32.16/0198

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Registration: 26 June 2019

10. DATE OF REVISION OF THE TEXT

Last revision: 05 September 2023

Registration number(s)

Kadcyla 100 mg	Botswana: S2 BOT2103704
	Namibia: NS2 21/26/0095
Kadcyla 160 mg	Botswana: S2 BOT2103705
	Namibia: NS2 21/26/0096

Approved Manufacturer:

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