NAME OF THE MEDICINE

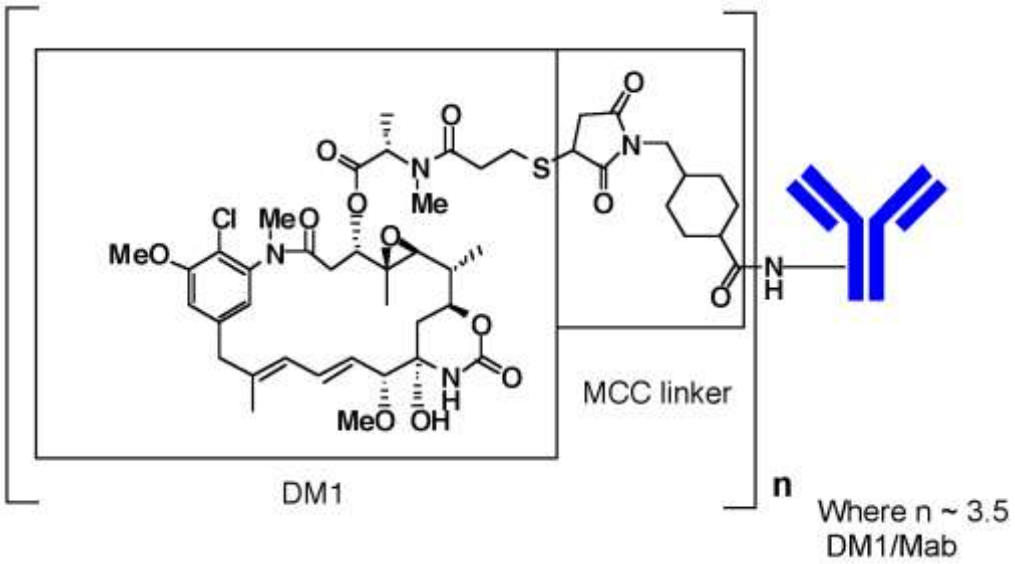
Kadcyla®

trastuzumab emtansine (rch)
CAS: 1018448-65-1

WARNING: Do not substitute Kadcyla for or with trastuzumab.
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 (Herceptin®).

Kadcyla (trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate that contains the humanized 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.

Trastuzumab emtansine has the following 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.

DESCRIPTION

Kadcyla is available as a single-use vial containing 100 mg or 160 mg of trastuzumab emtansine, with the following excipients: succinic acid, sodium hydroxide, sucrose and polysorbate 20.

PHARMACOLOGY

Pharmacodynamics

Trastuzumab emtansine is a HER2-targeted antibody-drug conjugate, containing the humanized anti-HER2 IgG1 antibody trastuzumab, covalently linked to the small molecule cytotoxin, DM1. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization 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 signaling 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 polymerization, both DM1 and Kadcyla cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death.

Pharmacokinetics

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 trial, EMILIA, who received 3.6 mg/kg of Kadcyla IV every 3 weeks, had a mean maximum serum concentration (Cmax) of trastuzumab emtansine of 83.4 (±16.5) μg/mL. 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 trial EMILIA, mean maximum DM1 levels in Cycle 1 following Kadcyla administration were consistently low and averaged 4.61 ± 1.61 ng/mL.

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

Excretion

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 Kadcyla 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 Kadcyla showed that age did not affect the pharmacokinetics of Kadcyla. No significant difference was observed in the pharmacokinetics of Kadcyla 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 Kadcyla showed that creatinine clearance (CLcr) does not affect pharmacokinetics of Kadcyla. Pharmacokinetics of Kadcyla 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 DMI1 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.

Kadcyla has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

CLINICAL TRIALS

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 (MBC) who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed within six months of completing adjuvant therapy. Prior to 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 min 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 1 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.

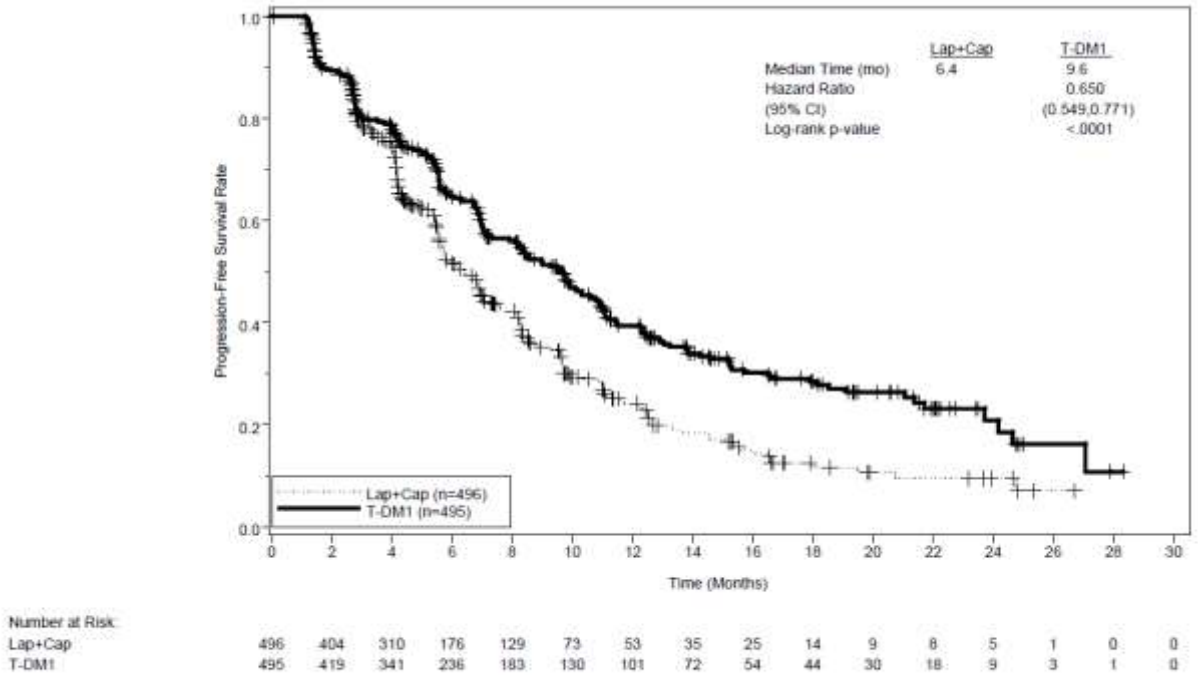
[b] The first interim analysis of overall survival (OS) was performed at the time of primary PFS analysis. Strong treatment effect was observed, but pre-specified efficacy boundary was not crossed. A second interim analysis for OS was conducted when 331 OS events were observed and the results are presented in this table.

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.

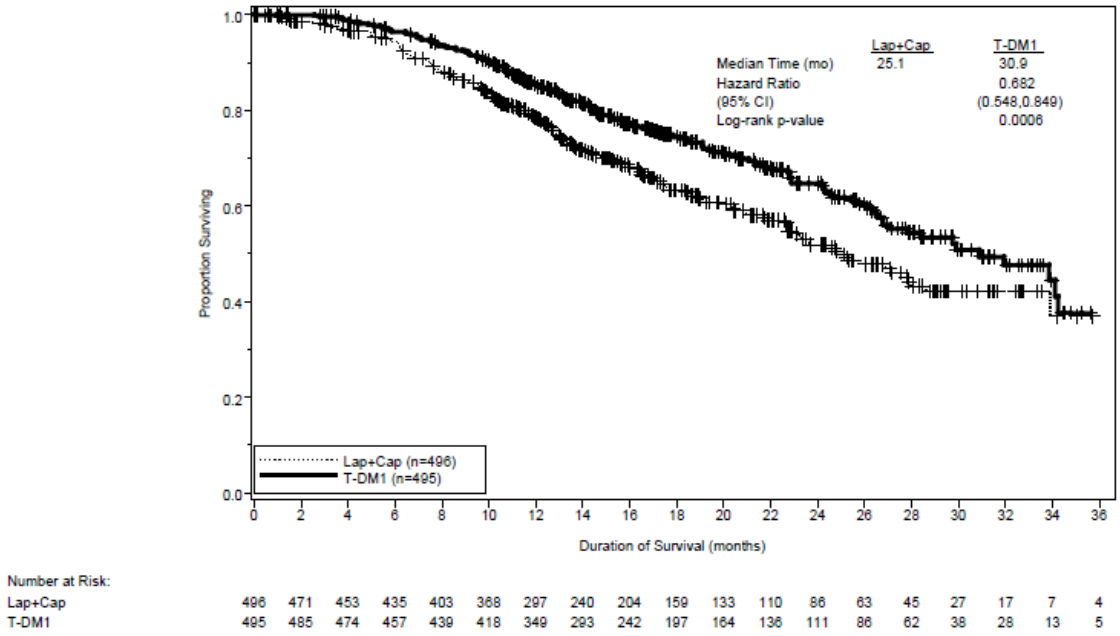
Of 495 patients who received Kadcyla in EMILIA, 65 patients (13%) were ≥ 65 years of age and 11 patients (2%) were ≥ 75 years of age. A trend for treatment benefit with Kadcyla compared to the control arm in terms of PFS for the subgroup of patients who were 65 to 74 years old was observed (total n=113; 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 1 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 2 Kaplan-Meier curve of overall survival



Number at Risk:

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

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

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

Patients (n=110) received 3.6 mg/kg of 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).

INDICATIONS

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.

CONTRAINDICATIONS

Kadcyla is contraindicated in patients with a known hypersensitivity to Kadcyla or any of its excipients (*see also Precautions; Infusion-Related Reactions and Hypersensitivity Reactions).*

PRECAUTIONS

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 Adverse 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.

Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities 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 Adverse 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 Dosage and Administration; Dose Modifications*). 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 Pharmacology, 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 Adverse 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. Treatment with Kadcyla has not been studied in patients with LVEF < 50% prior to initiation of treatment. Specific guidelines regarding dose modifications and discontinuation are provided in *Dosage and Administration; Dose Modifications*.

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, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia-have been reported in clinical trials of Kadcyla. In general, these symptoms were not severe *(see Adverse 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 Dosage and Administration, Dose Modifications*).

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 trastuzumab emtansine 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), the overall frequency of thrombocytopenia was 31.2% in the Kadcyla-treated group and 3.3% in the lapatinib plus capecitabine-treated group (see *Adverse Effects).* The incidence of $\geq$ 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 $\geq$ Grade 3 thrombocytopenia was 45.1% in the Kadcyla-treated group and 1.3% in the lapatinib plus capecitabine-treated group.

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. 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 *Dosage and Administration; Dose Modifications*.

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 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 drug administration.

Effects on the ability to drive and use machines
Studies on the effects on the ability to drive and use machines have not been performed.

On the basis of reported adverse reactions, Kadcyla is not expected to influence the ability to drive or use machines. Patients experiencing infusion-related reactions should be advised not to drive and use machines until symptoms abate.

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. Patients should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. 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 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 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 after concluding treatment.

Paediatric use

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

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 Clinical Trials, TDM4370g/BO21977 (EMILIA)*).

Based on a population pharmacokinetic analysis, age does not affect the pharmacokinetics of Kadcyla.

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

Trastuzumab emtansine has not been tested for carcinogenicity.

Effect on laboratory tests

Please see Precautions sections*; Hepatotoxicity and Thrombocytopenia.*

Use in renal impairment

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

Use in hepatic impairment

Please see *Pharmacology; Pharmacokinetics in Special Populations* and *Dosage and Administration.*

INTERACTIONS WITH OTHER MEDICINES

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 metabolized 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.

ADVERSE EFFECTS

Clinical Trials

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), not known (cannot be estimated from the available data).

Presented in the following table are adverse reactions that have been reported in association with the use of Kadcyla in clinical trials. The safety of Kadcyla has been evaluated in more than 1,871 patients.

Table 2 Summary of ADR's occurring in patients treated with Kadcyla

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

System Organ Class	All grades (%) n = 1871	Grade 3 - 5 (%) n = 1871	Frequency Category
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			
Fatigue	36.8	2.5	very common
Pyrexia	23.0	0.2	very common
Asthenia	16.3	1.1	very common
Chills	10.3	≤ 0.1	very common
Oedema peripheral	8.1	0.1	common
Hepatobiliary Disorders			
Hepatic failure	0.1	0.1	uncommon
Nodular regenerative hyperplasia	0.1	0.0	uncommon
Portal hypertension	0.3	0.1	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			
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	22.8	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

System Organ Class	All grades (%) n = 1871	Grade 3 - 5 (%) n = 1871	Frequency Category
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
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

The following table displays laboratory abnormalities observed in patients treated with Kadcyla in Study TDM4370/BO21977 (EMILIA).

Table 3 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

As with all therapeutic proteins, there is the potential for an immune response to Kadcyla. Among 836 patients from 6 clinical studies tested at multiple time points for anti-therapeutic antibody (ATA) responses to Kadcyla, 44 patients (5.3%) tested positive for antibodies to Kadcyla at one or more post-dose time points; 28 of these patients had negative baseline samples. The clinical significance of antibodies to Kadcyla is not yet known.

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

DOSAGE AND ADMINISTRATION

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

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 (HERCEPTIN).

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

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.

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.

Dosage

The recommended dose of Kadcyla is 3.6 mg/kg, administered as an IV infusion every 3 weeks until disease progression or unacceptable toxicity.

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 infusion may be administered at the rate the patient tolerated the most recent infusion.

Dose modifications

Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided below in Tables 4-8.

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

Table 4 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

Hepatotoxicity

Table 5 Dose Modification Guidelines for Increased Transaminases (AST/ALT)
(see Precautions; Hepatotoxicity)

Grade 2 (> 2.5 to ≤ 5 the ULN)	Grade 3 (>5 to ≤ 20 the ULN)	Grade 4 (> 20 x the ULN)
Treat at the same dose level	Do not administer Kadcyla until AST/ALT recovers to Grade ≤ 2, an then reduce one dose level.	Discontinue Kadcyla

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

Table 6 Dose Modification Guidelines for Hyperbilirubinemia
(See Precautions; Hepatotoxicity)

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

ULN = upper limit of normal

Thrombocytopenia

Table 7 Dose Modification Guidelines for Thrombocytopenia
(See Precautions; Thrombocytopenia)

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

Left Ventricular Cardiac Dysfunction

Table 8 Dose Modifications for Left Ventricular Cardiac Dysfunction
(See Precautions; Left Ventricular Dysfunction)

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

LVEF = left ventricular ejection fraction

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 Precautions; Use in the Elderly*).

Children: The safety and efficacy of Kadcyla in paediatric patients have not been established.

Renal impairment: No adjustment to the starting dose of Kadcyla is needed in patients with mild or moderate renal impairment (*see Pharmacology; 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 *Pharmacology, Pharmacokinetics in Special Populations*). Kadcyla was not 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 *Precautions, Hepatotoxicity*).

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 Sterile Water for Injection (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 trastuzumab emtansine / kg body weight (*see Dose Modifications for Dose Reduction Schedule*):

Volume (mL) = **Body weight** (kg) x **dose** (mg/kg)
20 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.

Instructions for administration

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 hrs at 2°C - 8°C (*see Storage Conditions*).

Administer the initial dose as a 90 min IV infusion. Patients should be observed during the infusion and for at least 90 min 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 Precautions; Extravasation)*.

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

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.

OVERDOSAGE

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; in New Zealand call 0800 764 766).

PRESENTATION AND STORAGE CONDITIONS

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 of trastuzumab emtansine.

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 SWFI should be used immediately following reconstitution. If not used immediately, the reconstituted vials can be stored for up to 24 hrs 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 hrs 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 Instructions for Administration).*

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

Disposal of unused/expired medicines

The release of medicines into the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

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Medical enquiries: 1800 233 950

Distributed in New Zealand by:
Roche Products (New Zealand) Limited
PO Box 109113
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NEW ZEALAND

Medical enquiries: 0800 656 464

POISON SCHEDULE OF THE MEDICINE

Australia: Schedule 4 - Prescription Only Medicine
New Zealand: Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

03 September 2013

DATE OF MOST RECENT AMENDMENT

12 December 2017