ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kadcyla 100 mg powder for concentrate for solution for infusion.
Kadcyla 160 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg single-use vial containing powder for concentrate for infusion solution delivers 5 mL of 20 mg/mL of trastuzumab emtansine after reconstitution (see section 6.6).

160 mg single-use vial containing powder for concentrate for infusion solution delivers 8 mL of 20 mg/mL of trastuzumab emtansine after reconstitution (see section 6.6).

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).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Kadcyla should only be prescribed by a physician and administered under the supervision of a healthcare professional who is experienced in the treatment of cancer patients.

Patients treated with trastuzumab emtansine 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 CE-marked In Vitro Diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2-status should be assessed by an alternate validated test.

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

Posology

The recommended dose of trastuzumab emtansine is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). Patients should be treated until disease progression or unacceptable toxicity.

The initial dose should be administered as a 90 minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion 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 the prior infusion was well tolerated, subsequent doses of trastuzumab emtansine may be administered as 30 minute infusions. Patients should be observed during the infusion and for at least 30 minutes after infusion.

The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions.

Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment should be available for immediate use (see section 4.4).

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 the dosing recommendations (see section 4.2, Posology).

Dose modification
Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided in text and Tables 1 to 5.

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

Table 1 Dose reduction schedule

Dose reduction schedule (Starting dose is 3.6 mg/kg)	**Dose to be administered**
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2 Dose modification guidelines for increased transaminases (AST/ALT)

Grade 2 (> 2.5 to ≤ 5 × the ULN)	**Grade 3 (> 5 to ≤ 20 × the ULN)**	**Grade 4 (> 20 × the ULN)**
No dose modification is required.	Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2 (>2.5 to ≤5 x ULN), and then dose reduce (see table 1).	Discontinue trastuzumab emtansine.

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

Table 3 Dose modification guidelines for hyperbilirubinemia

Grade 2 (> 1.5 to ≤ 3 × the ULN)	Grade 3 (> 3 to ≤ 10 × the ULN)	Grade 4 (> 10 × the ULN)
Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 (>ULN to 1.5x ULN). No dose modification is required.	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 (>ULN to 1.5x ULN), and then dose reduce (see table 1).	Discontinue trastuzumab emtansine.

ULN = upper limit of normal.

Table 4 Dose modification guidelines for thrombocytopenia

Grade 3 (Platelets: 25,000 to < 50,000/mm^3)	Grade 4 (Platelets: < 25,000/mm^3)
Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (i.e. platelets ≥ 75,000/mm^3). No dose modification is required.	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (i.e. platelets ≥ 75,000/mm^3), and then dose reduce (see table 1).

Table 5 Dose modifications for left ventricular dysfunction

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

LVEF = Left ventricular ejection fraction

Peripheral neuropathy
Trastuzumab emtansine 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).

Elderly patients
No dose adjustment is required in patients aged ≥ 65 years. There are insufficient data to establish the safety and efficacy in patients ≥ 75 years due to limited data in this subgroup. Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine (see sections 5.1 and 5.2).

Renal impairment
No adjustment to the starting dose 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. Trastuzumab emtansine 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 trastuzumab emtansine (see section 4.4 and 5.2).

Paediatric population
The safety and efficacy 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 metastatic breast cancer (MBC).

Method of administration

Trastuzumab emtansine must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

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

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 trastuzumab emtansine (see section 4.8). Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates.

It is recommended that treatment with trastuzumab emtansine 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
Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), has been observed during treatment with trastuzumab emtansine in clinical studies (see section 4.8). Transaminase elevations were generally transient with peak elevation at day 8 after administration of therapy and subsequent recovery to Grade 1 or less

prior to the next cycle. A cumulative effect 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 trastuzumab emtansine in the majority of the cases (see section 4.8).

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 trastuzumab emtansine. Observed cases may have been confounded by comorbidities and/or concomitant medicinal products with known hepatotoxic potential.

Liver function should be monitored prior to initiation of treatment and each dose. Patients with baseline elevation of ALT (e.g. due to liver metastases) 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.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine. 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, trastuzumab emtansine treatment must be permanently discontinued.

Trastuzumab emtansine has not been studied in patients with serum transaminases > 2.5 × ULN or total bilirubin > 1.5 × ULN prior to initiation of treatment. Treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN should 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 trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with trastuzumab emtansine, and therefore symptomatic congestive heart failure (CHF) is a potential risk (see section 4.8). General risk factors for a cardiac event and those identified in adjuvant breast cancer studies with trastuzumab therapy include advancing age (> 50 years), low baseline LVEF values (< 55%), low LVEF levels prior to or following the use of paclitaxel in the adjuvant setting, prior or concomitant use of antihypertensive medicinal products, previous therapy with an anthracycline and high BMI (> 25 kg/m^2).

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. In clinical studies, patients had a LVEF ≥ 50% at baseline. Patients with a history of congestive heart failure (CHF), serious cardiac arrhythmia requiring treatment, history of myocardial infarction or unstable angina within 6 months of randomization, or current dyspnoea at rest due to advanced malignancy were excluded from clinical studies. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see section 4.2).

Infusion-related reactions
Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR); treatment is not recommended for these patients. Patients should be observed closely for infusion-related reactions, especially during the first infusion.

Infusion-related reactions (due to cytokine release), characterized by one or more of the following symptoms have been reported: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia. In general, these symptoms were not severe (see section 4.8). In most

patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Treatment should be interrupted in patients with a severe IRR until signs and symptoms resolve. Consideration for re-treatment should be based on clinical assessment of the severity of the reaction. Treatment must be permanently discontinued in the event of a life threatening infusion-related reaction (see section 4.2).

Hypersensitivity reactions
Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients.

Patients should be observed closely for hypersensitivity/allergic reactions, which may have the same clinical presentation as an IRR. Serious, anaphylactic reactions have been observed in clinical studies with trastuzumab emtansine. Medicinal products 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 severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

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-coagulant 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 commonly reported with trastuzumab emtansine and was the most common adverse reaction leading to treatment discontinuation (see section 4.8). In clinical studies, the incidence and severity of thrombocytopenia were higher in Asian patients (see section 4.8).

It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Patients with thrombocytopenia ($\leq 100{,}000/mm^3$) and patients on anti-coagulant treatment (e.g. warfarin, heparin, low molecular weight heparins) should be monitored closely while on trastuzumab emtansine treatment. Trastuzumab emtansine 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 trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75{,}000/mm^3$) (see section 4.2).

Neurotoxicity
Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical studies with trastuzumab emtansine. Patients with Grade ≥ 3 peripheral neuropathy at baseline were excluded from clinical studies. Treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to $\leq$ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

Sodium content in excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception.

Pregnancy
There are no data from the use of trastuzumab emtansine in pregnant women. Trastuzumab, a component of trastuzumab emtansine, 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 component of trastuzumab emtansine, is expected to be teratogenic and potentially embryotoxic (see section 5.3).

Administration of trastuzumab emtansine to pregnant women is not recommended and women should be informed of the possibility of harm to the foetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended.

Breast-feeding
It is not known whether trastuzumab emtansine is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment.

Fertility
No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine.

4.7 Effects on ability to drive and use machines

Trastuzumab emtansine has no or negligible influence on the ability to drive and use machines. The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing infusion-related reactions should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The safety of trastuzumab emtansine has been evaluated in1871 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 trastuzumab emtansine were nausea, fatigue, and headache. 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.

Tabulated list of adverse reactions

The ADRs in1871 patients treated with trastuzumab emtansine are presented in Table 6. The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as 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 6 Tabulated list of ADRs in patients treated with trastuzumab emtansine

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia, Anaemia	Neutropenia, Leucopoenia	
Immune system disorders		Drug hypersensitivity	
Metabolism and nutrition disorders	Hypokalaemia		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral, Headache	Dizziness, Dysgeusia, Memory impairment	
Eye disorders		Dry eye, Conjunctivitis, Vision blurred, Lacrimation increased	
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			Hepatotoxicity, Hepatic failure, Nodular regenerative hyperplasia, Portal hypertension
Skin and subcutaneous tissue disorders	Rash	Pruritus, Alopecia, Nail disorder, Palmar-plantar erythrodysaesthesia syndrome, Urticaria	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Arthralgia, Myalgia		
General disorders and administration site conditions	Fatigue, Pyrexia, Asthenia, Chills	Peripheral oedema	Injection site extravasation
Investigations	Transaminases increased	Blood alkaline phosphatase increased	
Injury, poisoning and procedural complications		Infusion-related reactions	

Description of selected adverse reactions

Transaminases increased (AST/ALT)
Increase in serum transaminases (Grade 1-4) has been observed during treatment with trastuzumab emtansine in clinical studies (see section 4.4). Transaminase elevations were generally transient. A cumulative effect of trastuzumab emtansine on transaminases has been observed, and generally recovered when treatment was discontinued. Increased transaminases were reported in 24.2% of patients in clinical studies. Grade 3 or 4 increased AST and ALT were reported in 4.2% and 2.7% of patients respectively and usually occurred in the early treatment cycles (1-6). 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 trastuzumab emtansine exposure (AUC), trastuzumab emtansine 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 trastuzumab emtansine. 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. Additional LVEF monitoring is recommended for patients with LVEF ≤ 45% (See Table 5 in section 4.2 for specific dose modifications).

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 clinical studies with trastuzumab emtansine, with six Grade 3 and no Grade 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 clinical studies with trastuzumab emtansine, with one Grade 3 and one Grade 4 events reported. 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.

Haemorrhage
The incidence of severe haemorrhagic events (Grade ≥3) occurred in 2.2% of the overall trastuzumab emtansine treated patients in clinical studies. 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.

Thrombocytopenia
Thrombocytopenia or decreased platelet counts were reported in 24.9% of patients in clinical studies with trastuzumab emtansine and was the most common adverse reaction leading to treatment discontinuation (2.6%). 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 treated with trastuzumab emtansine. For dose modifications for thrombocytopenia, see sections 4.2 and 4.4.

Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response to trastuzumab emtansine. A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to trastuzumab emtansine. Following dosing,

5.3% (44/836) of patients tested positive for anti-trastuzumab emtansine antibodies at one or more post-dose time points. The clinical significance of anti-trastuzumab emtansine antibodies is not yet known.

Extravasation
Reactions secondary to extravasation have been observed in clinical studies with trastuzumab emtansine. 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 trastuzumab emtansine extravasation is unknown at this time.

Laboratory abnormalities

Table 7 displays laboratory abnormalities observed in patients treated with trastuzumab emtansine in clinical study TDM4370g/BO21977.

Table 7 Laboratory abnormalities observed in patients treated with trastuzumab emtansine in study TDM4370g/BO21977

Parameter	Trastuzumab emtansine		
	All Grades (%)	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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for trastuzumab emtansine overdose. In case of overdose, the patient should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted. 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 causal relationship to trastuzumab emtansine was not established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

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 polymerization, both DM1 and trastuzumab emtansine cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from *in vitro* cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.

- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

Clinical efficacy

TDM4370g/BO21977
A Phase III, randomised, multicentre, international, open-label clinical study was conducted in patients with HER2-positive unresectable locally advanced breast cancer (LABC) or MBC who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed during or within six months of completing adjuvant therapy. Only patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 were eligible. Prior to enrolment, breast tumour samples were required to be centrally confirmed for HER2-positive status defined as a score of 3 + by IHC or gene amplification by ISH. Baseline patient and tumour characteristics were well balanced between treatment groups. Patients with treated brain metastases were eligible for enrollment if they did not require therapy to control symptoms. For patients randomised to trastuzumab emtansine, the median age was 53 years, most patients were female (99.8%), the majority were Caucasian (72%), and 57% had oestrogen-receptor and/or progesterone-receptor positive disease. The study compared the safety and efficacy of trastuzumab emtansine with that of lapatinib plus capecitabine. A total of 991 patients were randomised to trastuzumab emtansine or lapatinib plus capecitabine as follows:

- Trastuzumab emtansine arm: trastuzumab emtansine 3.6 mg/kg intravenously over 30-90 minutes on Day 1 of a 21-day cycle
- Control arm (lapatinib plus capecitabine): lapatinib 1250 mg/day orally once per day of a 21-day cycle plus 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) and overall survival (OS) (see Table 8 and Figures 1 to 2).

Time to symptom progression, as defined by a 5-point decrease in the score derived from the Trials 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 study. A change of 5 points in the TOI-B is considered clinically significant. Kadcyla delayed patient-reported time to symptom progression for 7.1 months compared with 4.6 months for the control arm (Hazard Ratio 0.796 (0.667, 0.951); p-value 0.0121). The data are from an open-label study and no firm conclusions can be drawn.

Table 8 Summary of efficacy from study TDM4370g/BO21977 (EMILIA)

	Lapatinib + Capecitabine n = 496	**Trastuzumab emtansine n = 495**
Primary endpoints		
IRC-assessed progression-free survival (PFS)		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard ratio (stratified*)	0.650	
95% CI for Hazard ratio	(0.549, 0.771)	
p-value (Log-rank test, stratified*)	< 0.0001	
Overall Survival (OS)**		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard ratio (stratified*)	0.682	
95% CI for Hazard ratio	(0.548, 0.849)	
p-value (Log-rank test*)	0.0006	
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
Hazard ratio (95% CI)	0.658 (0.560, 0.774)	
p-value (Log-rank test*)	<0.0001	
Objective response rate (ORR)		
Patients with measurable disease	389	397
Number of patients with OR (%)	120 (30.8%)	173 (43.6%)
Difference (95% CI)	12.7% (6.0, 19.4)	
p-value (Mantel-Haenszel chi-squared test*)	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)

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; OR: objective response; IRC: independent review committee; HR: hazard ratios; CI: confidence interval

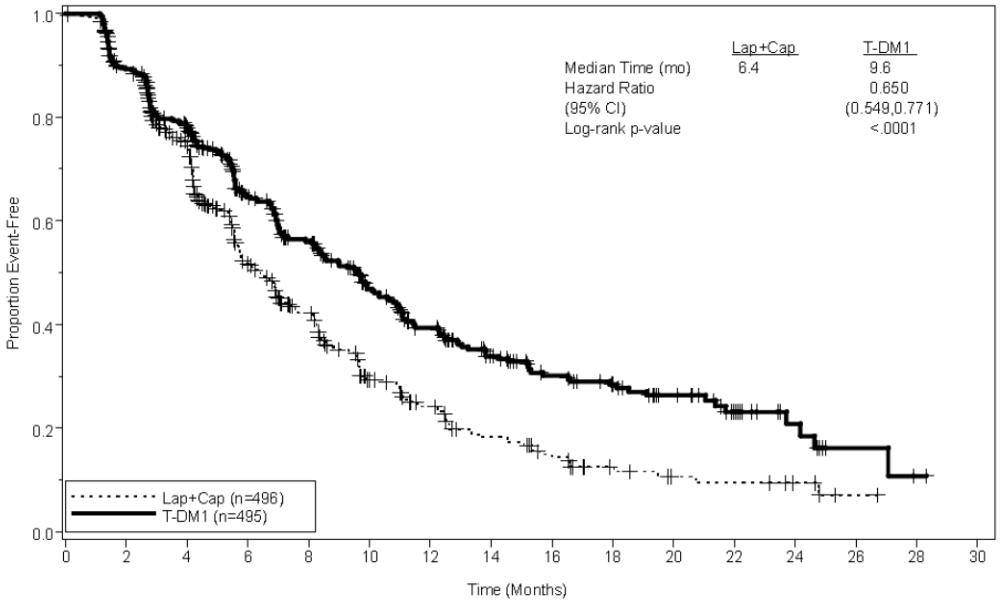
* Stratified by: world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 *vs.* > 1), and visceral *vs.* non-visceral disease.

** The interim analysis for OS was conducted when 331 events were observed. Since the efficacy boundary was crossed at this analysis, this is considered the definitive analysis.

A treatment benefit was seen in the subgroup of patients who had relapsed within 6 months of completing adjuvant treatment and had not received any prior systemic anti-cancer therapy in the metastatic setting (n=118); hazard ratios 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 trastuzumab emtansine 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.

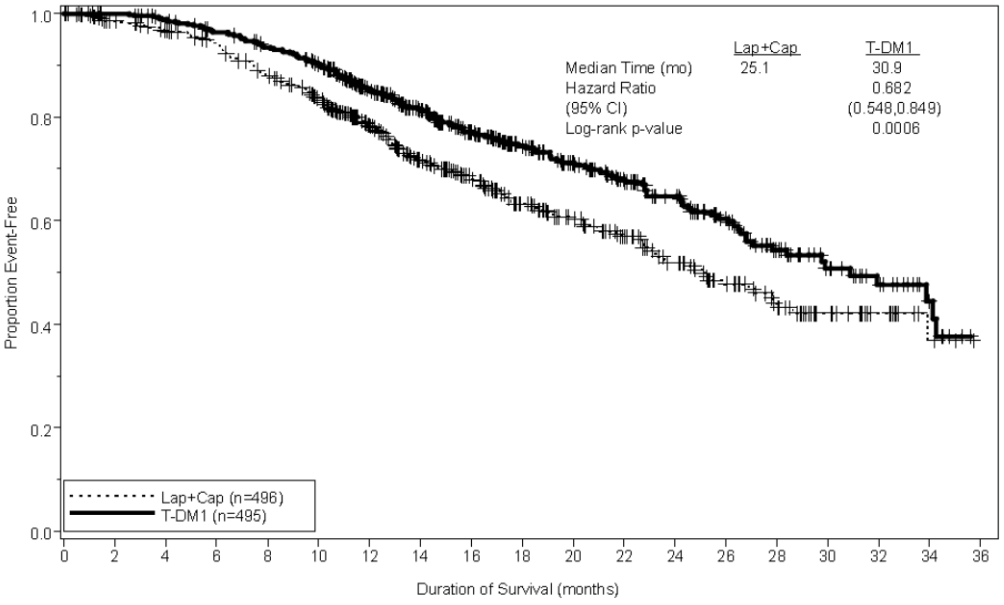
Figure 1 Kaplan-meier curve of IRC-assessed progression-free survival



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

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

Figure 2 Kaplan-meier curve of overall survival



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

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

In study TDM4370g/BO21977, consistent treatment benefit of trastuzumab emtansine was seen in the majority of pre-specified subgroups evaluated, supporting the robustness of the overall result. In the

subgroup of patients with hormone receptor-negative disease (n=426), the hazard ratios for PFS and OS were 0.56 (95% CI: 0.44, 0.72) and 0.75 (95% CI: 0.54, 1.03), respectively. In the subgroup of patients with hormone receptor-positive disease (n=545), the hazard ratios for PFS and OS were 0.72 (95% CI: 0.58, 0.91) and 0.62 (95% CI: 0.46, 0.85), respectively.

In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively. In patients ≥ 65 years old (n=138 across both treatment arms) the hazard ratios for progression-free survival (PFS) and Overall Survival (OS) were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. In patients 65 to 74 years old (n=113), based on IRC assessments, the hazard ratios for PFS and OS were 0.88 (95% CI: 0.53, 1.45) and 0.74 (95% CI: 0.37, 1.47), respectively. For patients 75 years or above, 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.

In the descriptive follow-up overall survival analysis, the hazard ratio was 0.75 (95% CI 0.64, 0.88). The median duration of overall survival was 29.9 months in the trastuzumab emtansine arm compared with 25.9 months in the lapatinib plus capecitabine arm. At the time of the descriptive follow-up overall survival analysis, a total of 27.4% of the patients had crossed over from the lapatinib plus capecitabine arm to the trastuzumab emtansine arm. In a sensitivity analysis censoring patients at the time of cross-over, the hazard ratio was 0.69 (95% CI 0.59, 0.82). The results of this descriptive follow-up analysis are consistent with the confirmatory OS analysis.

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

The primary endpoint was investigator assessed Progression-Free Survival (PFS). The median PFS was 9.2 months in the trastuzumab plus docetaxel arm and 14.2 months in the trastuzumab emtansine arm (hazard ratio, 0.59; p = 0.035), with a median follow-up of approximately 14 months in both arms. The objective response rate (ORR) was 58.0% with trastuzumab plus docetaxel and 64.2% with trastuzumab emtansine. The median duration of response was not reached with trastuzumab emtansine *vs.* 9.5 months in the control arm.

TDM4374g
A Phase II, single-arm, open-label study evaluated the effects of trastuzumab emtansine in patients with HER2-positive incurable, LABC 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 had 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 trastuzumab emtansine intravenously every 3 weeks until disease progression or unacceptable toxicity.

The key efficacy analyses were ORR based on independent radiologic review and duration of objective response. The ORR was 32.7% (95% CI: 24.1, 42.1), n = 36 responders, by both IRC and investigator review. The median duration of response by IRC was not reached (95% CI, 4.6 months to not estimable).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with trastuzumab emtansine in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Trastuzumab emtansine is administered intravenously. There have been no studies performed with other routes of administration.

Distribution
Patients in TDM4370g/BO21977 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. Based on population PK 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 deconjugation and catabolism by means of proteolysis in cellular lysosomes.

In vitro metabolism studies in human liver microsomes suggest that DM1, a small molecule component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and to a lesser extent by CYP3A5. DM1 did not inhibit major CYP450 enzymes in vitro. In human plasma, trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels. *In vitro,* DM1 was a substrate of P-glycoprotein (P-gp).

Elimination
Based on population pharmacokinetic (PK) analysis, following intravenous 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 intravenous infusion every 3 weeks.

Based on population PK analysis, body weight, albumin, sum of longest diameter of target lesions by Response Evaluation Criteria In Solid Tumors (RECIST), HER2 shed extracellular domain (ECD), baseline trastuzumab concentrations, and aspartate aminotransferase (AST) were identified as statistically significant covariates for trastuzumab emtansine PK parameters. However, the magnitude of effect of these covariates on trastuzumab emtansine exposure, suggests that these covariates are unlikely to have any clinically meaningful effect on trastuzumab emtansine exposure. In addition, exploratory analysis showed that the impact of covariates (i.e., renal function, race and age) on the pharmacokinetics of total trastuzumab and DM1 was limited and was not clinically relevant. In nonclinical studies, trastuzumab emtansine catabolites including DM1, Lys-MCC-DM1, and MCC-DM1 are mainly excreted in the bile with minimal elimination in urine.

Linearity/non-linearity
Trastuzumab emtansine when administered intravenously every 3 weeks exhibited linear PK 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.

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

Renal impairment
No formal PK study has been conducted in patients with renal impairment. The population PK analysis showed that creatinine clearance does not affect the PK of trastuzumab emtansine. Pharmacokinetics of trastuzumab emtansine in patients with mild (creatinine clearance CLcr 60 to 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 to 29 mL/min) are 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+ 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.

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

Other special populations
The population PK analysis showed that race did not appear to influence the PK of trastuzumab emtansine. Because most of the patients in trastuzumab emtansine clinical studies were females, the effect of gender on the PK of trastuzumab emtansine was not formally evaluated.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology
Administration of trastuzumab emtansine was well tolerated in rats and monkeys at doses up to 20 and 10 mg/kg, respectively, corresponding to 2040 μg DM1/m^2 in both species, which is approximately equivalent to the clinical dose of trastuzumab emtansine in patients. In the GLP toxicity studies, with the exception of irreversible peripheral axonal toxicity (observed only in monkeys at ≥ 10 mg/kg) and reproductive organ toxicity (observed only in rats at 60 mg/kg), partially or completely reversible dose dependent toxicities were identified in both animal models. Principal toxicities included liver (liver enzyme elevations) at ≥ 20 mg/kg and ≥ 10 mg/kg, bone marrow (reduced platelet and white blood cell count)/hematologic at ≥ 20 mg/kg and ≥ 10 mg/kg, and lymphoid organs at ≥ 20 mg/kg and ≥ 3 mg/kg, in rat and monkey, respectively.

Mutagenicity
DM1 was aneugenic or clastogenic in an *in vivo* single-dose rat bone marrow micronucleus assay at exposures that were comparable to mean maximum concentrations of DM1 measured in humans administered trastuzumab emtansine. DM1 was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Impairment of fertility and teratogenicity
Dedicated fertility studies have not been conducted with trastuzumab emtansine. However, based on results from general animal toxicity studies, adverse effects on fertility can be expected.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid
Sodium hydroxide
Sucrose
Polysorbate 20

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

3 years.

Shelf-life of the reconstituted solution
Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 24 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, the reconstituted vials can be stored for up to 24 hours at 2°C to 8°C, provided it was reconstituted under controlled and validated aseptic conditions, and must be discarded thereafter.

Shelf-life of the diluted solution
The reconstituted Kadcyla solution diluted in infusion bags containing sodium chloride 9 mg/ml (0.9%) solution for infusion, or sodium chloride 4.5 mg/ml (0.45%) solution for infusion, is stable for up to 24 hours at 2°C to 8°C, provided it was prepared under controlled and validated aseptic conditions. Particulates may be observed on storage if diluted in 0.9% sodium chloride (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Kadcyla is provided in 15 ml (100 mg) or 20 ml (160 mg) Type 1 glass vial closed with a grey-butyl rubber stopper coated with fluoro-resin laminate, and sealed with an aluminium seal with a white or purple plastic flip-off cap.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

The reconstituted Kadcyla solution should be diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin infusion bags.

The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required for the infusion when the concentrate for infusion is diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion.

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

Instructions for reconstitution

- 100 mg trastuzumab emtansine vial: Using a sterile syringe, slowly inject 5 mL of sterile water for injection into the vial.
- 160 mg trastuzumab emtansine vial: Using a sterile syringe, slowly inject 8 mL of sterile water for injection into the 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, or is cloudy or discoloured.

Instructions for dilution
Determine the volume of the reconstituted solution required based on a dose of 3.6 mg trastuzumab emtansine/kg body weight (see section 4.2):

$$\textbf{Volume}\ (\text{mL}) = \frac{\textit{Total dose to be administered}\ (\textbf{body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg}))}{\textbf{20}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of sodium chloride 4.5 mg/ml (0.45%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion. Glucose (5%) solution should not be used (see section 6.2). Sodium chloride 4.5 mg/ml (0.45%) solution for infusion may be used without a polyethersulfone (PES) 0.20 or 0.22-µm in-line filter. If sodium chloride 9 mg/ml (0.9%) solution for infusion is used for infusion, a 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required. Once the infusion is prepared it should be administered immediately. Do not freeze or shake the infusion during storage.

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/885/001
EU/1/13/885/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Ltd.
Lonzastrasse
CH-3930 Visp
Switzerland

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the content and format of the Kadcyla educational material and a communication plan with the National Competent Authority in the Member State before Kadcyla is launched in each Member State.

The MAH shall ensure that in parallel to the launch of Kadcyla, all health care professionals who may prescribe, dispense or administer Kadcyla and/or Herceptin are provided with a health care professional (HCP) educational pack. This HCP educational pack shall consist of the following:

- Kadcyla SPC
- Health care professional information

The HCP information shall contain the following key messages:

1. Kadcyla and Herceptin are two very different products with different active substances never to be used interchangeably. Kadcyla is NOT a generic version of Herceptin and has different properties, indications and dose.
2. Kadcyla is an antibody-drug conjugate containing humanized anti-HER2 IgG1 antibody trastuzumab and DM1, a microtubule-inhibitory maytansinoid.
3. Do not substitute or combine Kadcyla with or for Herceptin
4. Do not administer Kadcyla in combination with chemotherapy
5. Do not administer Kadcyla at doses greater than 3.6 mg/kg once every 3 weeks
6. If a prescription for Kadcyla is written electronically, it is important to ensure that the medication prescribed is trastuzumab emtansine and not trastuzumab.
7. Both the invented name Kadcyla and its full non-proprietary name (trastuzumab emtansine) should be used and confirmed when prescribing, preparing the infusion solution and administering Kadcyla to patients. It must be verified that the non-proprietary name is trastuzumab emtansine.
8. In order to prevent medication errors it is important to review the Summary of Product Characteristics and to check the outer carton and vial labels to ensure that the medicinal product being prepared and administered is Kadcyla and not Herceptin.
9. Description of the key differences between Kadcyla and Herceptin in relation to indication, dose, administration and packaging differences.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kadcyla 100 mg powder for concentrate for solution for infusion
trastuzumab emtansine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

100 mg single-use vial containing powder for concentrate for infusion solution delivers 5 mL of 20 mg/mL of trastuzumab emtansine after reconstitution.

3. LIST OF EXCIPIENTS

Excipients:
Succinic acid, sodium hydroxide, sucrose, polysorbate 20.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial of 100 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8ºC)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/885/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kadcyla 100 mg powder for concentrate for solution for infusion
trastuzumab emtansine
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution and dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kadcyla 160 mg powder for concentrate for solution for infusion
trastuzumab emtansine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

160 mg single-use vial containing powder for concentrate for infusion solution delivers 8 mL of 20 mg/mL of trastuzumab emtansine after reconstitution

3. LIST OF EXCIPIENTS

Excipients:
Succinic acid, sodium hydroxide, sucrose, polysorbate 20.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial of 160 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8ºC)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/885/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kadcyla 160 mg powder for concentrate for solution for infusion
trastuzumab emtansine
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution and dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

160 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Kadcyla100 mg powder for concentrate for solution for infusion
Kadcyla 160 mg powder for concentrate for solution for infusion
trastuzumab emtansine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start being given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kadcyla is and what it is used for

What Kadcyla is
Kadcyla contains the active substance trastuzumab emtansine, which is made up of two parts that are linked together:
- trastuzumab - a monoclonal antibody that binds selectively to an antigen (a target protein) called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When trastuzumab binds to HER2 it can stop the cancer cells growth and cause them to die.
- DM1 – an anti-cancer substance that becomes active once Kadcyla enters the cancer cell.

What Kadcyla is used for
Kadcyla is used to treat breast cancer in adults when:
- the cancer cells have many HER2 proteins on them - your doctor will test your cancer cells for this.
- you have already received the medicine trastuzumab and a medicine known as a taxane.
- the cancer has spread to areas near the breast or to other parts of your body

2. What you need to know before you are given Kadcyla

You must not be given Kadcyla
- if you are allergic to trastuzumab emtansine or any of the other ingredients of this medicine (listed in section 6).

You should not be given Kadcyla if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given Kadcyla.

Warnings and precautions
Talk to your doctor or nurse before you are given Kadcyla if:
- you have ever had a serious infusion-related reaction from using trastuzumab characterised by symptoms such as flushing, chills, fever, shortness of breath, difficulty breathing, rapid heartbeat or a drop in blood pressure.
- you are receiving treatment with blood thinning medicines (e.g. warfarin, heparin).
- you have any history of liver problems. Your doctor will check your blood to test your liver function before and regularly during treatment

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you are given Kadcyla.

Look out for side effects
Kadcyla can make some existing conditions worse, or cause side effects. See section 4 for more details about what side effects to look out for.

Tell your doctor or nurse straight away if you notice any of the following serious side effects while you are given Kadcyla:

- **Breathing problems:** Kadcyla can cause serious breathing problems such as shortness of breath (either at rest or while performing any type of activity) and cough. These may be signs of inflammation of your lung, which may be serious, and even fatal. If you develop lung disease your doctor may stop treatment with this medicine.

- **Liver problems:** Kadcyla can cause inflammation or damage to cells in the liver that can stop the liver from functioning normally. Inflamed or injured liver cells may leak higher than normal amounts of certain substances (liver enzymes) into the bloodstream, resulting in elevated liver enzymes in blood tests. In most cases you will not have any symptoms. Some symptoms could be yellowing of your skin and whites of your eyes (jaundice). Your doctor will check your blood to test your liver function before and regularly during treatment.

  Another rare abnormality that can occur in the liver is a condition known as nodular regenerative hyperplasia (NRH). This abnormality causes the structure of the liver to change and can change how the liver functions. Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.

- **Heart problems:** Kadcyla can weaken the heart muscle. When the heart muscle is weak, patients may develop symptoms such as shortness of breath at rest or when sleeping, chest pain, swollen legs or arms, and a sensation of rapid or irregular heartbeats. Your doctor will check your heart function before and regularly during treatment. You should tell your doctor immediately if you notice any of the above symptoms.

- **Infusion-related reactions or allergic reactions**: Kadcyla can cause flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing during the infusion or after the infusion on the first day of treatment. Your doctor or nurse will check to see whether you are having any of these side effects. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

- **Bleeding problems:** Kadcyla can lower the number of platelets in your blood. Platelets help your blood to clot so you might get unexpected bruising or bleeding (such as nose bleeds, bleeding from gums). Your doctor will check your blood regularly for decreased platelets. You should tell your doctor immediately if you notice any unexpected bruising or bleeding.

- **Neurological problems:** Kadcyla can damage nerves. You may experience tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet. Your doctor will monitor you for signs and symptoms of neurological problems.

Tell your doctor or nurse straight away if you notice any of the side effects above.

Children and adolescents
Kadcyla is not recommended for anyone under the age of 18 years. This is because there is no information on how well it works in this age group.

Other medicines and Kadcyla
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking:
- any medicines to thin your blood such as warfarin or decrease the ability to form blood clot such as aspirin
- medicines for fungal infections called ketoconazole, itraconazole or voriconazole
- antibiotics for infections called clarithromycin or telithromycin
- medicines for HIV called atazanavir, indinavir, nelfinavir, ritonavir or saquinavir.
- medicine for depression called nefazodone

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you are given Kadcyla.

Pregnancy
Kadcyla is not recommended if you are pregnant because this medicine may cause harm to the unborn baby.
- Tell your doctor before using Kadcyla if you are pregnant, think you may be pregnant or are planning to have a baby.
- Use effective contraception to avoid becoming pregnant while you are being treated with Kadcyla.. Talk to your doctor about the best contraception for you.
- You should continue to take your contraception for at least 7 months after your last dose of Kadcyla. Talk to your doctor before stopping your contraception.
- Male patients or their female partners should also use effective contraception.
- If you do become pregnant during treatment with Kadcyla, tell your doctor straight away.

Breast-feeding
You should not breast-feed during treatment with Kadcyla. Also you should not breast-feed for 7 months after your last infusion of Kadcyla. It is not known whether the ingredients in Kadcyla pass into breast-milk. Talk to your doctor about this.

Driving and using machines
It is not expected that Kadcyla will affect your ability to drive, cycle, use tools or machines. If you experience flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat (infusion-related reaction), blurred vision, tiredness, headache, or dizziness, do not drive, cycle, use tools or machines until these reactions stop.

Important information about some of the ingredients of Kadcyla
This medicine contains less than 1 mmol sodium (23 mg) per dose. It is essentially ‘sodium- free’.

3. How you are given Kadcyla

Kadcyla will be given to you by a doctor or nurse in a hospital or clinic:
- It is given by a drip into a vein (intravenous infusion).
- You will be given one infusion every 3 weeks.

How much you will be given
- You will be given 3.6 mg of Kadcyla for every kilogram of your body weight. Your doctor will calculate the correct dose for you.
- The first infusion will be given to you over 90 minutes. You will be observed by a doctor or nurse while it is being given and for at least 90 minutes following the initial dose, in case you have any side effects.
- If the first infusion is well tolerated, the infusion on your next visit may be given over 30 minutes. You will be observed by a doctor or nurse while it is being given and for at least 30 minutes following the dose, in case you have any side effects.
- The total number of infusions that you will be given depends on how you respond to the treatment.
- If you experience side effects, your doctor may decide to continue your treatment but lower your dose, delay the next dose or stop the treatment.

If you miss a Kadcyla treatment
If you forget or miss your Kadcyla appointment, make another appointment as soon as possible. Do not wait until your next planned visit.

If you stop Kadcyla treatment
Do not stop treatment with this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse straight away if you notice any of following serious side effects.

Very common (may affect more than 1 in 10 people):
- Kadcyla may cause inflammation or damage to cells in the liver, resulting in elevated liver enzymes in blood tests. However, in most cases during Kadcyla treatment, liver enzyme levels are elevated mildly and temporarily, do not cause any symptoms, and do not affect liver function.
- Unexpected bruising and bleeding (such as nose bleeds).
- Tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet. These symptoms may indicate nerve damage.

Common (may affect up to 1 in 10 people):
- Flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat during the infusion or up to 24 hours after the infusion – these are so-called infusion-related reactions.
- Heart problems can occur. Most patients will not have symptoms from the heart problems. If symptoms do occur, cough shortness of breath at rest or when sleeping flat, chest pain and swollen ankles or arms, a sensation of rapid or irregular heartbeats may be observed.

Uncommon (may affect up to 1 in 100 people):
- Inflammation of your lungs can cause breathing problems such as shortness of breath (either at rest or while performing any type of activity), coughing or coughing spells with a dry cough – these are signs of inflammation of your lung tissue.
- Your skin and whites of your eyes get yellow (jaundice) – these could be signs of severe liver damage.
- Allergic reactions can occur and most patients will have mild symptoms such as itching or tightness in the chest. In more severe cases, swelling of your face or tongue, trouble swallowing or difficulty breathing may occur.

Tell your doctor or nurse straight away if you notice any of the serious side effects above.

Other side effects include

Very common:
- decreased red blood cells (shown in a blood test)
- being sick (vomiting)
- diarrhoea
- dry mouth
- urinary tract infection
- constipation
- stomach ache
- cough
- shortness of breath
- inflammation of the mouth
- chills or flu like symptoms
- decrease in your potassium levels (shown in a blood test)
- difficulty sleeping
- muscle or joint pain
- fever
- headache
- skin rashes
- feeling tired
- weakness

Common:
- decreased white blood cells (shown in a blood test)
- dry eyes, watery eyes or blurred vision
- eye redness or infection
- indigestion
- swelling of legs and/or arms
- bleeding from the gums
- increase in blood pressure
- feeling dizzy
- taste disturbances
- itching
- difficulty in remembering
- hair loss
- hand-and-foot skin reaction (Palmar-plantar erythrodysaesthesia syndrome)
- nail disorder

Uncommon:
- Another abnormality that can be caused by Kadcyla is a condition known as nodular regenerative hyperplasia of the liver. This abnormality causes the structure of the liver to change. Patients develop multiple nodules in the liver that can change how the liver functions. Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.
- If the Kadcyla infusion solution leaks into the area around the infusion site you may develop tenderness or redness of your skin, or swelling at the infusion site.

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

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kadcyla

Kadcyla will be stored by the health professionals at the hospital or clinic.

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator at (2°C - 8°C). Do not freeze.
- When prepared as a solution for infusion Kadcyla is stable for up to 24 hours at 2°C to 8°C, and must be discarded thereafter.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kadcyla contains
- The active substance is trastuzumab emtansine.
- Each 100 mg single-use vial containing powder for concentrate for infusion solution designed to deliver 5 ml of 20 mg/ml of trastuzumab emtansine.
- Each 160 mg single-use vial containing powder for concentrate for infusion solution designed to deliver 8 ml of 20 mg/ml of trastuzumab emtansine.
- The other ingredients are succinic acid, sodium hydroxide (see section 2 under ‘Important information about some of the ingredients of Kadcyla’), sucrose, and polysorbate 20.

What Kadcyla looks like and contents of the pack
- Kadcyla is a white to off-white lyophilised powder for concentrate for solution for infusion supplied in glass vials.
- Kadcyla is available in packs containing 1 vial.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

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

Kadcyla must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.

Always keep this medicine in the closed original pack at a temperature of 2ºC – 8 ºC in a refrigerator. A vial of Kadcyla reconstituted with water for injections (not supplied) is stable for 24 hours at 2ºC – 8 ºC after reconstitution and must not be frozen.

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

The reconstituted Kadcyla solution should be diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin infusion bags.

The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required for the infusion when the concentrate for infusion is diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion.

Instructions for reconstitution

- Kadcyla 100mg: using a sterile syringe, slowly inject 5 mL of sterile water for injection into the 100 mg trastuzumab emtansine vial.
- Kadcyla 160mg: using a sterile syringe, slowly inject 8 mL of sterile water for injection into the 160 mg trastuzumab emtansine 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 reconstituted solution is cloudy or discoloured.

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

Instructions for dilution
Determine the volume of the reconstituted solution required based on a dose of 3.6 mg trastuzumab emtansine/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textit{Total dose to be administered} = (\textbf{body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg}))}{\textbf{20}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of sodium chloride 4.5 mg/ml (0.45%) solution for infusion or sodium chloride 9 mg/ml (0.9%) solution for infusion. Glucose (5%) solution should not be used Sodium chloride 4.5 mg/ml (0.45%) solution for infusion may be used without a polyethersulfone (PES) 0.20 or 0.22-µm in-line filter. If sodium chloride 9 mg/ml (0.9%) solution for infusion is used for infusion, a 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required. Once the infusion is prepared it should be administered immediately. Do not freeze or shake the infusion during storage. If diluted aseptically, it may be stored for up to 24 hours at 2°C to 8°C.