▼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 "Reporting of suspected adverse reactions" for how to report adverse reactions.

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. **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.160 mg single-use vial containing powder for concentrate for infusion solution delivers 8 mL of 20 mg/mL of trastuzumab emtansine after reconstitution. 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). **PHARMACEUTICAL FORM:** Powder for concentrate for solution for infusion.White to off-white lyophilised powder. **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. **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. 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. 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.
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. *Dose modification.* Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Kadcyla as per guidelines provided in text. Kadcyla dose should not be re-escalated after a dose reduction is made. Dose reduction schedule (Starting dose is 3.6 mg/kg). First dose reduction: 3 mg/kg. Second dose reduction: 2.4 mg/kg. Requirement for further dose reduction: discontinue treatment. Dose modification guidelines for increased transaminases (AST/ALT) (ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal). Grade 2 (> 2.5 to ≤ 5 ´ the ULN): No dose modification is required.Grade 3 (> 5 to ≤ 20 ´ the ULN): Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2 (>2.5 to ≤5 x ULN), and then dose reduce. Grade 4 (> 20 ´ the ULN): Discontinue trastuzumab emtansine. Dose modification guidelines for hyperbilirubinemia. Grade 2 (> 1.5 to ≤ 3 ´ the ULN): Do not administer trastuzumab emtansine until total bilirubin recovers to Grade £ 1 (>ULN to 1.5x ULN). No dose modification is required. Grade 3 (> 3 to ≤ 10 ´ the ULN): Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 (>ULN to 1.5x ULN), and then dose reduce. Grade 4 (> 10 ´ the ULN): Discontinue trastuzumab emtansine. Dose modification guidelines for thrombocytopenia. Grade 3 (Platelets: 25,000 to < 50,000/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. 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), and then dose reduce. Dose modifications for left ventricular dysfunction (LVEF = Left ventricular ejection fraction). LVEF < 40%: Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue trastuzumab emtansine. LVEF > 45%: Continue treatment with trastuzumab emtansine. LVEF 40% to ≤ 45% and decrease is < 10% points from baseline: Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline: 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. Symptomatic CHF: Discontinue trastuzumab emtansine. *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. *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. *Renal impairment.* No adjustment to the starting dose is needed in patients with mild or moderate renal impairment. 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. *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. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **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. The ADRs in1871 patients treated with trastuzumab emtansine are listed below. 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. Very Common: urinary tract infection, thrombocytopenia, anaemia, hypokalaemia, insomnia, neuropathy peripheral, headache, haemorrhage, epistaxis, cough, dyspnoea, stomatitis, diarrhoea, vomiting, nausea, constipation, dry mouth, abdominal pain, rash, musculoskeletal pain, arthralgia, myalgia, fatigue, pyrexia, asthenia, chills, transaminases increased. Common: neutropenia, leucopoenia, drug hypersensitivity, dizziness, dysgeusia, memory impairment, dry eye, conjunctivitis, vision blurred, lacrimation increase, left ventricular dysfunction, hypertension, dyspepsia, gingival bleeding, pruritus, alopecia, nail disorder, palmar-plantar erythrodysaesthesia syndrome, urticaria, peripheral oedema, blood alkaline phosphatase increased, infusion-related reactions. Uncommon: pneumonitis (ILD), hepatotoxicity, hepatic failure, nodular regenerative hyperplasia, portal hypertension, injection site extravasation.
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. 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. *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%. *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. *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. *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. The incidence of severe haemorrhagic events (Grade ≥3) occurred in 2.2% of the overall trastuzumab emtansine treated patients and 1.8% of Asian trastuzumab emtansine treated patients. In some of the observed cases the patients were also receiving anti-coagulation therapy. Cases of bleeding events with a fatal outcome have been observed. *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. Laboratory abnormalities observed in patients treated with trastuzumab emtansine in clinical study TDM4370g/BO21977. Parameter Hepatic: Increased bilirubin: All Grades: 21%; Grade 3: <1%; Grade 4: 0%. Increased AST: All Grades: 98%; Grade 3: 8%; Grade 4: <1%. Increased ALT: All Grades: 82%; Grade 3: 5%; Grade 4: <1%. Parameter Haematologic: Decreased platelets: All Grades: 85%; Grade 3: 14%; Grade 4: 3%. Decreased haemoglobin: All Grades: 63%; Grade 3: 5%; Grade 4: 1%. Decreased neutrophils: All Grades: 41%; Grade 3: 4%; Grade 4: <1%. Parameter Potassium: Decreased potassium: All Grades: 35%; Grade 3: 3%; Grade 4: <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 (see details below). België/Belgique: Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie, EUROSTATION II Victor Hortaplein 40/40 B-1060 Brussel, Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be. Agence fédérale des médicaments et des produits de santé Division Vigilance, EUROSTATION II Place Victor Horta 40/40 B-1060 Bruxelles, Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be. Luxembourg : Direction de la Santé Division de la Pharmacie et des Médicaments, Villa Louvigny Allée Marconi L-2120 Luxembourg, Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. **MARKETING AUTORISATION HOLDER:** Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom. **MARKETING AUTORISATION NUMBER(S):** EU/1/13/885/001, EU/1/13/885/002. **DATE OF FIRST AUTHORISATION:** 15 November 2013. **DATE OF REVISION OF THE TEXT:** 25/02/2016. On presription. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. R.E. Dr Chr. Lenaerts - BE/KAD/0816/0006 -11/08/2016