Herceptin IV + SC

NAME OF THE MEDICINAL PRODUCT: Herceptin 150 mg powder for concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION:** One vial contains 150 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures. The reconstituted Herceptin solution contains 21 mg/mL of trastuzumab. **PHARMACEUTICAL FORM:** Powder for concentrate for solution for infusion. White to pale yellow lyophilised powder. **Therapeutic indications:** Breast cancer. Metastatic breast cancer. Herceptin is indicated for the treatment of adult patients with HER2positive metastatic breast cancer (MBC):- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.-in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.-in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. Early breast cancer Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC) - following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable), - following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel, -in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin, - in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. **Posology and method of administration:** MBC. ***Three-weekly schedule.*** The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. ***Weekly schedule.*** The recommended initial loading dose of Herceptin is 4 mg/kg body weight. The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose. ***Administration in combination with paclitaxel or docetaxel.*** In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of Herceptin (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of Herceptin if the preceding dose of Herceptin was well tolerated. ***Administration in combination with an aromatase inhibitor.*** In the pivotal trial (BO16216) Herceptin and anastrozole were administered from day 1. There were no restrictions on the relative timing of Herceptin and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors). EBC. ***Three-weekly and weekly schedule.*** As a three-weekly regimen the recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. Breast cancer (MBC and EBC). ***Duration of treatment.*** Patients with MBC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first: extending treatment in EBC beyond one year is not recommended. ***Dose reduction.*** No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays. If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. ***Missed doses.*** If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively. If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively. ***Special populations.*** Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition. ***Paediatric population.*** There is no relevant use of Herceptin in the paediatric population. ***Method of administration.*** Herceptin loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Herceptin intravenous infusion should be administered by a health-care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. **Contraindications:** Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients. Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

NAME OF THE MEDICINAL PRODUCT: Herceptin 600 mg solution for injection in vial.
QUALITATIVE AND QUANTITATIVE COMPOSITION: One vial of 5 mL contains 600 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures. **PHARMACEUTICAL FORM:** Solution for injection Clear to opalescent solution, colourless to yellowish. **Therapeutic indications:** Breast cancer ***Metastatic breast cancer.*** Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC): as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. In combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable. In combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. ***Early breast cancer*** .Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC). Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. In combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. **Posology and method of administration.** The recommended dose for Herceptin subcutaneous formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 25 minutes every three weeks. In the pivotal trial (BO22227) Herceptin subcutaneous formulation was administered in the neoadjuvant/adjuvant setting in patients with early breast cancer. The preoperative chemotherapy regimen consisted of docetaxel (75 mg/m^2) followed by FEC (5FU, epirubicin and cyclophosphamide) at a standard dose. ***Duration of treatment.*** Patients with MBC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended. ***Dose reduction.*** No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the Summary of Product Characteristics (SmPC) for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays. If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. ***Missed doses.*** If the patient misses a dose of Herceptin subcutaneous formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive Herceptin subcutaneous formulation administrations should not be less than three weeks. ***Special populations.*** Dedicated pharmacokinetic studies in older people and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition. ***Paediatric population.*** There is no relevant use of Herceptin in the paediatric population. ***Method of administration.*** The 600 mg dose should be administered as a subcutaneous injection only over 25 minutes. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Herceptin subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions. **Contraindications:** Hypersensitivity to trastuzumab, murine proteins, hyaluronidase or to any of the other excipients. Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

SUMMARY OF PRODUCT CHARACTERISTICS Herceptin IV 150mg & Herceptin SC 600 mg solution for injection in vial.
HER2 testing is mandatory prior to initiation of therapy. Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy and should be administered by a healthcare professional only. It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only. Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulations and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982. In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine.). **Undesirable effects:** Amongst the most serious and/or common adverse reactions reported in Herceptin usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, administration-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions. The safety profile of Herceptin subcutaneous formulation (evaluated in 298 and 297 patients treated with the intravenous and subcutaneous formulations respectively) from the pivotal trial in EBC was overall similar to the known safety profile of the intravenous formulation. Severe adverse events (defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE grade ≥3) version 3.0) were equally distributed between both Herceptin formulations (52.3 % versus 53.5 % in the intravenous formulation versus subcutaneous formulation respectively). Some adverse events / reactions were reported with a higher frequency for the subcutaneous formulation: ***Serious adverse events*** (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation): 14.1 % for the intravenous formulation versus 21.5 % for the subcutaneous formulation. The difference in serious adverse events rates between formulations was mainly due to infections with or without neutropenia (4.4 % versus 8.1 %) and cardiac disorders (0.7 % versus 1.7 %); ***Post-operative wound infections*** (severe and/or serious): 1.7 % versus 3.0 % for the intravenous formulation versus subcutaneous formulation, respectively; ***Administration-related reactions***: 37.2 % versus 47.8 % for the intravenous formulation versus subcutaneous formulation, respectively during the treatment phase; ***Hypertension:*** 4.7 % versus 9.8 % for the intravenous formulation versus subcutaneous formulation respectively. The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The following are adverse reactions that have been reported in association with the use of intravenous Herceptin alone or in combination with chemotherapy in pivotal clinical trials (N = 8386) and in the post-marketing setting. All the terms included are based on the highest percentage seen in pivotal clinical trials. **Infections and infestations**. Very common: infection, nasopharyngitis. Common: neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, pharyngitis. Uncommon: sepsis. **Neoplasms benign, malignant and unspecified (incl. cysts and polyps).** Not known: malignant neoplasm progression, neoplasm progression. **Blood and lymphatic system disorders.** Very common: febrile neutropenia, anaemia, neutropenia, white blood cell count decreased/leukopenia, thrombocytopenia. Not known: hypoprothrombinaemia, immune thrombocytopenia. **Immune system disorders.** Common: hypersensitivity. Not known: +anaphylactic reaction,+anaphylactic shock. **Metabolism and nutrition disorders.** Very common: weight decreased/weight loss, anorexia. Not known: hyperkalaemia. **Psychiatric disorders.** Very common: insomnia. Common: anxiety, depression, thinking abnormal. **Nervous system disorders.** Very common: [1]tremor, dizziness, headache, paraesthesia, dysgeusia. Common: peripheral neuropathy, hypertonia, somnolence, ataxia. Rare: paresis. Not known: brain oedema. **Eye disorders.** Very common: conjunctivitis, lacrimation increased. Common: dry eye. Not known: papilloedema, retinal haemorrhage. **Ear and labyrinth disorders.** Uncommon: deafness. **Cardiac disorders.** Very common: [1]blood pressure decreased, [1]blood pressure increased, [1]heart beat irregular, [1]palpitation, [1]cardiac flutter, ejection fraction decreased*. Common: +cardiac failure (congestive), [+1]supraventricular tachyarrhythmia, cardiomyopathy. Uncommon: pericardial effusion. Not known: cardiogenic shock, pericarditis, bradycardia, gallop rhythm present. **Vascular disorders.** Very common: hot flush. Common: [+1]hypotension, vasodilatation. **Respiratory, thoracic and mediastinal disorders.** Very common: [+1]wheezing, +dyspnea, cough, epistaxis, rhinorrhea. Common: +pneumonia, asthma, lung disorder, +pleural effusion. Rare: pneumonitis. Not known: +pulmonary fibrosis, +respiratory distress, +respiratory failure, +lung infiltration, +acute pulmonary oedema, +acute respiratory distress syndrome, +bronchospasm, +hypoxia, +oxygen saturation decreased, laryngeal oedema, orthopnoea, pulmonary oedema, interstitial lung disease. **Gastrointestinal disorders.** Very common: diarrhea, vomiting, nausea, [1] lip swelling, abdominal pain, dyspepsia, constipation, stomatitis. Common: haemorrhoids, dry mouth. **Hepatobiliary disorders.** Common: hepatocellular injury, hepatitis, liver tenderness. Rare: jaundice. Not known: hepatic failure. **Skin and subcutaneous tissue disorders.** Very common: erythema, rash, [1]swelling face, alopecia, nail disorder, palmar-plantar erythrodysaesthesia syndrome. Common: acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis. Uncommon: urticaria. Not known: angioedema. **Musculoskeletal and connective tissue disorders.** Very common: arthralgia, [1]muscle tightness, myalgia. Common: arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity. **Renal and urinary disorders.** Common: Renal disorder. Not known: glomerulonephritis membranous, glomerulonephropathy, renal failure. **Pregnancy, puerperium and perinatal conditions.** Not known: oligohydramnios, renal hypoplasia, pulmonary hypoplasia. **Reproductive system and breast disorders.** Common: breast inflammation/mastitis. **General disorders and administration site conditions.**Very common: asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion related reaction, pain, pyrexia, mucosal inflammation, peripheral oedema. Common: malaise, oedema. **Injury, poisoning and procedural complications.** Common: contusion. + Denotes adverse reactions that have been reported in association with a fatal outcome. [1] Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.* Observed with combination therapy following anthracyclines and combined with taxanes. Description of selected adverse reactions. ***Cardiac dysfunction.*** Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Herceptin. It has been associated with a fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin. In 3 pivotal EBC clinical trials of adjuvant intravenous Herceptin given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic congestive heart failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially after a taxane (0.3-0.4 %). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited. When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6 %. Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of Herceptin.In the pivotal metastatic trials of intravenous Herceptin, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide (27 %), and was significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving Herceptin and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF. ***Administration related reactions/hypersensitivity.*** Administration related reactions (ARRs)/hypersensitivity reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache were seen in Herceptin clinical trials. The rate of ARRs of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy. Anaphylactoid reactions have been observed in isolated cases. ***Haematotoxicity.*** Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy. ***Pulmonary events.*** Severe pulmonary adverse reactions occur in association with the use of Herceptin and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency. ***Immunogenicity*** In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1 % (30/296) of patients treated with Herceptin intravenous developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm. The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy (determined by pathological Complete Response [pCR] and event free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous. There are no immunogenicity data available for Herceptin in gastric cancer. Description of selected adverse reactions with the subcutaneous formulation. ***Administration-related reactions.*** In the pivotal trial, the rate of all grade ARRs was 37.2 % with the Herceptin intravenous formulation and 47.8 % with the Herceptin subcutaneous formulation; severe grade 3 reactions were reported in 2.0 % and 1.7 % of the patients, respectively during the treatment phase; no severe grade 4 or 5 reactions were observed. All of the severe ARRs with the Herceptin subcutaneous formulation occurred during concurrent administration with chemotherapy. The most frequent severe reaction was drug hypersensitivity. The systemic reactions included hypersensitivity, hypotension, tachycardia, cough, and dyspnoea. The local reactions included erythema, pruritus, oedema, rash and pain at the site of the injection. ***Infections.*** The rate of severe infections (NCI CTCAE grade ≥3) was 5.0 % versus 7.1 %, in the Herceptin intravenous formulation arm and the Herceptin subcutaneous formulation arm respectively. The rate of serious infections (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation) was 4.4 % in the Herceptin intravenous formulation arm and 8.1 % in the Herceptin subcutaneous formulation arm. The difference between formulations was mainly observed during the adjuvant treatment phase (monotherapy) and was mainly due to postoperative wound infections, but also to various other infections such as respiratory tract infections, acute pyelonephritis and sepsis. They resolved within a mean of 13 days in the Herceptin intravenous treatment arm and a mean of 17 days in the Herceptin subcutaneous treatment arm. ***Hypertensive events.*** In the pivotal trial BO22227, there were more than twice as many patients reporting all grade hypertension with the Herceptin subcutaneous formulation (4.7 % versus 9.8 % in the intravenous and subcutaneous formulations respectively), with a greater proportion of patients with severe events (NCI CTCAE grade ≥3) <1 % versus 2.0 % the intravenous and subcutaneous formulations respectively. All but one patient who reported severe hypertension had a history of hypertension before they entered the study. Some of the severe events occurred on the day of the injection. ***Immunogenicity.*** In the neoadjuvant-adjuvant setting EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with Herceptin intravenous and 15.9 % (47/295) of patients receiving Herceptin subcutaneous vial developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm and 3 of 47 in the Herceptin subcutaneous arm, 21.0 % of patients treated with Herceptin subcutaneous formulation developed antibodies against the excipient hyaluronidase (rHuPH20). The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy (determined by pathological Complete Response [pCR] and event free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous formulation and Herceptin subcutaneous. **Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa** Study MO22982 investigated switching between the Herceptin intravenous and Herceptin subcutaneous formulation with a primary objective to evaluate patient preference for either the intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomized to one of two different three-weekly Herceptin treatment sequences (IV [Cycles 1-4]→ SC [Cycles 5-8], or SC [Cycles 1-4]→ IV [Cycles 5-8]). Patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%). For the sequence IV→SC (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8% vs. 56.4%, respectively; for the sequence SC→IV (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4% vs. 48.7%, respectively. Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<5%) and similar to post-switching rates (Cycles 5-8). No grade 4 or grade 5 adverse events were reported. **Special warnings and precautions for use.** ***Traceability*** In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded. **Reporting of suspected adverse reactions**. If a pregnancy occurs while using Herceptin or within 7 months following the last dose of Herceptin, please immediately report the pregnancy to the Local Adverse Event Line at +32 2 525 82 99. 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 here below. ***België/Belgique.*** Federaal agentschap voor geneesmiddelen en gezondheidsproducten/Agence fédérale des médicaments et des produits de santé - Afdeling Vigilantie - Division Vigilance EUROSTATION II, Place Victor Hortaplein, 40/ 40 - B-1060 Brussel/ Bruxelles - Website: www.fagg.be/ 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 AUTHORISATION HOLDER:** Roche Registration GmbH; Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany **MARKETING AUTHORISATION NUMBER(S): Herceptin IV** EU/1/00/145/001; **Herceptin SC** EU/1/00/145/002. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** Date of first authorisation: 28 August 2000. Date of latest renewal: 28 August 2010. **DATE OF REVISION OF THE TEXT: Herceptin IV: 06/04/2018. Herceptin SC: 06/04/2018. Delivery**: on medical prescription. 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/ONCO/0418/0023 – 25/04/2018

PERJETA

Enhanced Safety Reporting for Potential Perjeta-Exposed Pregnancies
- PERJETA should be avoided during pregnancy. There is limited amount of data from the use of PERJETA in pregnant women and the safe use of PERJETA during pregnancy and lactation has not been established.
- Verify pregnancy status prior to the initiation of PERJETA. Women of child bearing potential should use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA.
- Monitor patients who become pregnant during PERJETA therapy or within 6 months following the last dose of PERJETA closely for oligohydramnios.
- If PERJETA is used during pregnancy or if a patient becomes pregnant while being treated with PERJETA or within 6 months following the last dose of PERJETA, immediately report exposure to the Roche Drug Safety line at **+32 2 525 82 99**.
- Additional information will be requested during a PERJETA-exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of PERJETA and to provide appropriate information to HA, HCP's and patients.

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

NAME OF THE MEDICINAL PRODUCT: Perjeta 420 mg concentrate for solution for infusion**. QUALITATIVE AND QUANTITATIVE COMPOSITION:** One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml. After dilution, one ml of solution contains approximately 3.02 mg of pertuzumab for the initial dose and approximately 1.59 mg of pertuzumab for the maintenance dose. Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology. **PHARMACEUTICAL FORM:** Concentrate for solution for infusion. Clear to slightly opalescent, colourless to pale yellow, liquid. **Therapeutic indications**: ***Metastatic breast cancer*** Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. ***Neoadjuvant treatment of breast cancer*** Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. **Posology and method of administration:** Perjeta is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available. Posology: Patients treated with Perjeta must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test. To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures. The recommended initial loading dose of pertuzumab is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. When administered with pertuzumab the recommendation is to follow a 3 weekly schedule for trastuzumab administered as either: an IV infusion with an initial loading dose of

trastuzumab 8 mg/kg body weight followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight; or a fixed subcutaneous dose of trastuzumab by injection (600 mg) every 3 weeks irrespective of the patient's body weight. When administered with pertuzumab the recommended initial dose of docetaxel is 75 mg/m², administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m² on subsequent cycles if the initial dose is well tolerated (the docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and pertuzumab). The medicinal products should be administered sequentially and not mixed in the same infusion bag. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, this should be administered after Perjeta and trastuzumab. An observation period of 30 to 60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel. ***Metastatic breast cancer*** Patients should be treated with Perjeta and trastuzumab until disease progression or unmanageable toxicity. ***Neoadjuvant treatment of breast cancer*** Perjeta should be administered for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment. ***Delayed or missed doses Perjeta*** If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule. If the time between two sequential infusions is 6 weeks or more, the loading dose of 840 mg Perjeta IV should be re-administered as a 60-minute infusion, followed by a maintenance dose of 420 mg IV administered over a period of 30 to 60 minutes every 3 weeks thereafter. ***Delayed or missed doses trastuzumab IV*** If the time between two sequential infusions is less than 6 weeks, the 6 mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule. If the time between two sequential infusions is 6 weeks or more, the loading dose of 8 mg/kg of trastuzumab IV should be re- administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered over a period of 30 or 90 minutes every 3 weeks thereafter. ***Delayed or missed doses trastuzumab SC*** If the time between two sequential infusions is more than 3 weeks the fixed dose of 600mg trastuzumab SC should be administered as soon as possible. Do not wait until the next planned dose. ***Dose modification*** Dose reductions are not recommended for Perjeta. Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. For docetaxel and other chemotherapy dose modifications, see relevant SmPC. For trastuzumab, dose reductions are not recommended, see trastuzumab SmPC. If trastuzumab treatment is discontinued, treatment with Perjeta should be discontinued. If docetaxel is discontinued, treatment with Perjeta and trastuzumab may continue until disease progression or unmanageable toxicity in the metastatic setting. ***Left ventricular dysfunction*** Perjeta and trastuzumab should be withheld for at least 3 weeks for any of the following: signs and symptoms suggestive of congestive heart failure (Perjeta should be discontinued if symptomatic heart failure is confirmed) a drop in left ventricular ejection fraction (LVEF) to less than 40% a LVEF of 40%-45% associated with a fall of ≥ 10% points below pre-treatment values. Perjeta and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with < 10% points below pretreatment value. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. ***Elderly patients*** Limited data are available on the safety and efficacy of Perjeta in patients ≥ 65 years of age. No significant differences in safety and efficacy of Perjeta were observed between elderly patients aged 65 to 75 years and adult patients aged < 65 years. No dose adjustment is necessary in the elderly population ≥ 65 years of age. Very limited data are available in patients > 75 years of age. ***Renal impairment*** Dose adjustments of pertuzumab are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available. ***Hepatic impairment*** The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment. No specific dose recommendations can be made. ***Paediatric population*** The safety and efficacy of Perjeta in children and adolescents below 18 years of age have not been established. There is no relevant use of Perjeta in the paediatric population in the indication of breast cancer. Method of administration: Perjeta is administered intravenously by infusion. It should not be administered as an intravenous push or bolus. For instructions on dilution of Perjeta prior to administration. For the initial dose, the recommended infusion period is 60 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes to 60 minutes. ***Infusion reactions*** The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion may be resumed when symptoms abate. Treatment including oxygen, beta agonists, antihistamines, rapid i.v. fluids and antipyretics may also help alleviate symptoms. ***Hypersensitivity reactions/anaphylaxis*** The infusion should be discontinued immediately and permanently if the patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Undesirable effects**: Summary of the safety profile: The safety of Perjeta has been evaluated in more than 2,000 patients in the randomized trials CLEOPATRA (n=808), NEOSPHERE (n=417), and TRYPHAENA (n=225) and in Phase I and phase II trials conducted in patients with various malignancies and predominantly treated with Perjeta in combination with other antineoplastic agents. The safety of Perjeta in Phase I and II studies (including the BERENICE trial) was generally consistent with that observed in the CLEOPATRA, NEOSPHERE and TRYPHAENA trials, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether Perjeta was administered as monotherapy or with concomitant anti-neoplastic agents. The ADRs in patients treated with Perjeta in the metastatic and neoadjuvant setting are listed below by MedDRA system organ class (SOC) and categories of frequency: Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon(≥ 1/1,000 to < 1/100) Rare (≥ 1/10,000 to < 1/1,000) Very rare (< 1/10,000) Not known (cannot be estimated from the available data). Infections and infestations: Very common: Upper respiratory tract infection, Nasopharyngitis, Common: Paronychia; Blood and lymphatic system: Very common: Febrile neutropenia*, Neutropenia, Leucopenia, Anaemia; Immune system disorders: Very common: Hypersensitivity/anaphylactic reaction°, Infusion reaction/cytokine release syndrome°°; Metabolism and nutrition disorders Very common: Decreased appetite †; Psychiatric disorders: Very common: Insomnia; Nervous system disorders: Very common: Neuropathy peripheral, Headache †, Dysgeusia; Common: Peripheral sensory neuropathy, Dizziness; Eye disorders: Common: Lacrimation increased; Cardiac disorders: Common: Left ventricular dysfunction † (including congestive heart failure)**; Respiratory, thoracic and mediastinal disorders: Very common: Cough†, Common: Pleural effusion, Dyspnoea †, Uncommon: Interstitial lung disease; Gastrointestinal disorders Very common: Diarrhoea †, Vomiting †, Stomatitis, Nausea †, Constipation †, Dyspepsia; Skin and subcutaneous tissue disorders: Very common Alopecia, Rash †, Nail disorder, Common: Pruritus, Dry skin; Musculoskeletal and connective tissue disorders: Very common: Myalgia, Arthralgia; General disorders and administration site conditions: Very common: Mucositis/mucosal inflammation, Pain †, Oedema† , Pyrexia, Fatigue †, Asthenia †, Common: Chills. *Including adverse reactions with a fatal outcome. **For the overall treatment period across the 3 studies. †Except for febrile neutropenia, neutropenia, leucopenia, lacrimation increased, interstitial lung disease, paronychia, and alopecia, all events in this table were also reported in at least 1% of patients participating in Perjeta monotherapy trials, although not necessarily considered causally related to Perjeta by the investigator. Very common events (reported in ≥ 10% of Perjeta monotherapy-treated patients) are marked in the Table with a †. °Hypersensitivity/anaphylactic reaction is based on a group of terms. °°Infusion reaction/cytokine release syndrome includes a range of different terms within a time window, see "Description of selected adverse reactions" below. Description of selected adverse reactions: ***Left ventricular dysfunction*** In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of LVD during study treatment was higher in the placebo-treated group than in the Perjeta-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta-treated group (1.8% in the placebo-treated group vs. 1.5% in the Perjeta-treated group). In the neoadjuvant trial NEOSPHERE , in which patients received 4 cycles of Perjeta as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the Perjeta, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and trastuzumab-treated group. In the neoadjuvant trial TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus trastuzumab and FEC (followed by Perjeta plus trastuzumab and docetaxel); 9.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC (this excludes a patient who experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus trastuzumab and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel experienced symptomatic LVD. In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense doxorubin and cyclophosphamide (AC) followed by Perjeta plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by Perjeta plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus trastuzumab and docetaxel. ***Infusion reactions*** An infusion reaction was defined in the pivotal trial CLEOPATRA in metastatic breast cancer reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of Perjeta was given the day before trastuzumab and docetaxel to allow for the examination of Perjeta-associated reactions. On the first day when only Perjeta was administered, the overall frequency of infusion reactions was 9.8% in the placebo-treated group and 13.2% in the Perjeta-treated group, with the majority of infusion reactions being mild or moderate. The most common infusion reactions (≥ 1.0%) in the Perjeta-treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity and vomiting. During the second cycle when all medicinal products were administered on the same day, the most common infusion reactions in the Perjeta-treated group (≥ 1.0%) were fatigue, dysgeusia, drug hypersensitivity, myalgia and vomiting. In the NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, Perjeta was administered on the same day as other study treatments in all cycles. Infusion reactions were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with a majority of reactions being mild or moderate. ***Hypersensitivity reactions/anaphylaxis*** In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of investigator reported hypersensitivity/anaphylaxis events during the entire treatment period was 9.3% in the placebo-treated group and 11.3% in the Perjeta-treated group, of which 2.5% and 2.0% were NCI-CTCAE Grade 3-4, respectively. Overall, 2 patients in the placebo-treated group and 4 patients in the Perjeta-treated group experienced events described as anaphylaxis by the investigator. Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to the study treatment, most reactions were assessed as secondary to docetaxel infusions. In NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In TRYPHAENA, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2%), of which 2.6% were NCI-CTCAE v.3 Grade 3-4. ***Febrile neutropenia*** In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (63.0% of patients in the Perjeta-treated group and 58.3% of patients in the placebo-treated group), of which the majority were neutropenic events. Febrile neutropenia occurred in 13.7% of Perjeta-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed among Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (25.8%) compared with the placebo-treated group (11.3%). In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant trastuzumab and docetaxel. ***Diarrhoea*** In the pivotal trial CLEOPATRA in metastatic breast cancer, diarrhoea occurred in 68.4% of Perjeta-treated patients and 48.7% of placebo-treated patients. Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 9.3% in Perjeta-treated patients vs 5.1% in placebo-treated patients. The median duration of the longest episode was 18 days in Perjeta-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents. In the NEOSPHERE trial, diarrhoea occurred in 45.8% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 33.6% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. In both studies most events were mild to moderate in severity. ***Rash*** In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of Perjeta-treated patients, compared with 38.9% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne. In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta + TCH and 20.0% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. ***Laboratory abnormalities*** In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of NCI-CTCAE (version 3) Grade 3-4 neutropenia was balanced in the two treatment groups (86.3% of Perjeta-treated patients and 86.6% of placebo-treated patients, including 60.7% and 64.8% Grade 4 neutropenia, respectively). In the NEOSPHERE trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 74.5% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 84.5% in patients treated with trastuzumab and docetaxel, including 50.9% and 60.2% Grade 4 neutropenia, respectively. In the TRYPHAENA trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 85.3% in patients treated with neoadjuvant Perjeta + TCH and 77.0% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC, including 66.7% and 59.5% Grade 4 neutropenia, respectively. 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: België/Belgique: Federaal agentschap voor geneesmiddelen en gezondheidsproducten/Agence fédérale des médicaments et des produits de santé, Afdeling Vigilantie/Division Vigilance, EUROSTATION II, Place Victor Hortaplein, 40/ 40, B-1060 Brussel/Bruxelles, Website: www.fagg.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/actvites/pharmacie-medicament/index.html. **MARKETING AUTHORISATION HOLDER**: Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany **MARKETING AUTHORISATION NUMBER(S):** EU/1/13/813/001 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** 04/03/2013 **DATE OF REVISION OF THE TEXT:** 30/04/2018 On prescription Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu BE/ONCO/0518/0029 – 22/05/2018 – R.E.: Dr. Chr. Lenaerts

Kadcyla

▼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 antibodydrug 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[Nmaleimidomethyl] cyclohexane1carboxylate). **PHARMACEUTICAL FORM:** Powder for concentrate for solution for infusion.White to offwhite 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 (21day 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 infusionrelated 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 infusionrelated symptoms. Trastuzumab emtansine should be discontinued in case of lifethreatening 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 3week 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 reescalated 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 x the ULN): No dose modification is required.Grade 3 (> 5 to ≤ 20 x 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 x the ULN): Discontinue trastuzumab emtansine. Dose modification guidelines for hyperbilirubinemia. Grade 2 (> 1.5 to ≤ 3 x 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 x 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 x the ULN): Discontinue trastuzumab emtansine. Dose modification guidelines for thrombocytopenia. Grade 3 (Platelets: 25,000 to < 50,000/mm³): Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (i.e. platelets ≥ 75,000/mm³). No dose modification is required. Grade 4 (Platelets: < 25,000/mm³): Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (i.e. platelets ≥ 75,000/mm³), 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 14) 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 (16). In general, the Grade ≥ 3 hepatic events were not associated with poor clinical outcome; subsequent followup 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%. *Infusionrelated reactions.* Infusionrelated reactions are characterised by one or more of the following symptoms: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia. Infusionrelated reactions were reported in 4.0% of patients in clinical studies with trastuzumab emtansine, with six Grade 3 and no Grade 4 events reported. Infusionrelated 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. *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/mm3), with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥ 75,000/mm3) 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/mm3) was 8.7% in patients treated with trastuzumab emtansine. *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 antitherapeutic antibody (ATA) responses to trastuzumab emtansine. Following dosing, 5.3% (44/836) of patients tested positive for antitrastuzumab emtansine antibodies at one or more postdose 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/actvites/pharmacie-medicament/index.html. **MARKETING AUTORISATION HOLDER:** Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany. **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:** 16/03/2018. 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/ONCO/0318/0019 – 29/03/2018