**▼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:** 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. 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. Posology: The recommended initial loading dose of Perjeta 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 Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight. When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m$^2$, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m$^2$ 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 Perjeta). 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* If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta should be administered as soon as possible without regard to the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial loading dose of 840 mg Perjeta should be re-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. *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. *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 *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. *Patients with renal impairment* Dose adjustments of Perjeta 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. *Patients with 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. **Contraindications:** Hypersensitivity to pertuzumab 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. *Metastatic Breast Cancer* In the pivotal clinical trial CLEOPATRA, 408 patients received at least one dose of Perjeta in combination with trastuzumab and docetaxel. The most common (ADRs ≥ 50%) seen with Perjeta in combination with trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE (v. 3) Grade 3-4 ADRs (> 10%) were neutropenia, febrile neutropenia and leucopenia, and the most common serious adverse events were febrile neutropenia, neutropenia and diarrhoea. Treatment-related deaths occurred in 1.2% of patients in the Perjeta-treated group and 1.5% of patients in the placebo-treated group and were mainly due to febrile neutropenia and/or infection. In the pivotal trial CLEOPATRA, ADRs were reported less frequently after discontinuation of docetaxel treatment. After discontinuation of docetaxel, ADRs in the Perjeta and trastuzumab treated group occurred in < 10% of patients with the exception of diarrhoea (28.1%), upper respiratory tract infection (18.3%), rash (18.3%), headache (17.0%), fatigue (13.4%), nasopharyngitis (17.0%), asthenia (13.4%), pruritus (13.7%), arthralgia (11.4%), nausea (12.7%), pain in extremity (13.4%), back pain (12.1%) and cough (12.1%). *Neoadjuvant Treatment of Breast Cancer* In the neoadjuvant trial NEOSPHERE, the most common ADRs (≥50%) seen with Perjeta in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADR (≥10%) was neutropenia. In the neoadjuvant trial TRYPHAENA, when Perjeta was administered in combination with trastuzumab and FEC (5-fluorouracil, epirubicin, cyclophosphamide) for 3 cycles followed by 3 cycles of Perjeta, trastuzumab and docetaxel, the most common ADRs (≥50%) were neutropenia, diarrhoea and nausea. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia and leucopenia. When Perjeta was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide), the most common ADRs (≥50%) were diarrhoea, nausea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia and leucopenia. Similarly, when Perjeta was administered in combination with TCH (docetaxel, carboplatin and trastuzumab) for 6 cycles, the most common ADRs (≥50%) were diarrhoea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia, anaemia, leucopenia and diarrhoea. The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established. In the BERENICE trial, when Perjeta was administered in combination with trastuzumab and paclitaxel for four cycles following four cycles of two weekly doxorubicin and cyclophosphamide (dose dense AC), the most common ADRs (≥50%) were nausea, diarrhoea, fatigue and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADR (≥10%) was neutropenia. When Perjeta was administered in combination with trastuzumab and docetaxel for four cycles following four cycles of FEC the most common ADRs (≥50%) were nausea, diarrhea and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADRs (≥10%) were febrile neutropenia and diarrhoea. The overall safety profile seen in BERENICE is consistent with that observed in previous data in the neoadjuvant setting for NEOSPHERE and TRYPHAENA. 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 the other study treatment drugs 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 via the national reporting system listed here. 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/activites/pharmacie-medicament/index.html. **MARKETING AUTHORISATION HOLDER**: Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom **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:** 20/07/2017 Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu BE/ONCO/0817/0038 – 24/08/2017