

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 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:** 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 2-5 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/m²) 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 2-5 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 Kadcycla (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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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: 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: blood pressure decreased, blood pressure increased, heart beat irregular, palpitation, cardiac flutter, ejection fraction decreased*. Common: cardiac failure (congestive), supraventricular tachyarrhythmia, cardiomyopathy. Uncommon: pericardial effusion. Not known: cardiogenic shock, pericarditis, bradycardia, gallop rhythm present. **Vascular disorders.** Very common: hot flush. Common: hypotension, vasodilatation. **Respiratory, thoracic and mediastinal disorders.** Very common: wheezing, dyspnea, cough, epistaxis, rhinorrhoea. 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, lip swelling, abdominal pain, dyspepsia, constipation, stomatitis. Common: pancreatitis, 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, swelling face, alopecia, nail disorder, palmar-plantar erythrodysesthesia syndrome. Common: acne, dry skin, ecchymosis, hyperhidrosis, maculopapular rash, pruritus, onychoclasia, dermatitis. Uncommon: urticaria. Not known: angioedema. **Musculoskeletal and connective tissue disorders.** Very common: arthralgia, 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: confusion. * Denotes adverse reactions that have been reported in association with a fatal outcome. † 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 ARR 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 treatment setting, 8.1 % (24/296) of patients treated with Herceptin intravenous developed antibodies against trastuzumab (regardless of antibody presence at baseline). Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 Herceptin intravenous patients. The clinical relevance of these antibodies is not known; nevertheless the pharmacokinetics, efficacy (determined by pathological Complete Response [pCR]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous did not appear to be adversely affected by these antibodies. 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 ARR 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 ARR 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 treatment, 8.1 % (24/296) of patients treated with Herceptin intravenous and 14.9 % (44/295) of patients receiving Herceptin subcutaneous vial developed antibodies against trastuzumab (regardless of antibody presence at baseline). Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 Herceptin intravenous and 4 of 44 Herceptin subcutaneous vial patients, 20.0 % of patients treated with Herceptin subcutaneous formulation developed antibodies against the excipient hyaluronidase (rHuPH20). The clinical relevance of these antibodies is not known; nevertheless the pharmacokinetics, efficacy (determined by pathological Complete Response [pCR]) and safety determined by occurrence of administration related reactions (ARRs) of Herceptin intravenous formulation and Herceptin subcutaneous formulation did not appear to be adversely affected by these antibodies. **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 In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file. **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 Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom **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: 10/03/2017. Herceptin SC: 18/02/2016. **Delivery:** of 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/HERC/0317/0001 - 22/03/2017