PROPOSAL

FOR THE INCLUSION OF TRASTUZUMAB

IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

FOR THE TREATMENT OF HER2-POSITIVE BREAST CANCER

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1. Summary statement of the proposal for inclusion, change or deletion

Breast cancer is an urgent global health priority. In 2008, almost 1.4 million women were diagnosed with breast cancer according to Globocan; and nearly 500,000 of them died from the disease that year. In just two decades, the annual incidence is predicted to be as high as 2.7 million; the current prevalence is already above 5 million with much of the burden lying in developing countries experiencing an epidemiological transition. A United Nations High-Level Meeting on non-communicable disease prevention and control put the spotlight on non-communicable diseases (NCDs) as social and economic issues; with a crucial focus on cancer and newer strategies to enable access to essential medicines for cancers this decade. In that context, we lay our rationale for qualifying trastuzumab, a critical medicine for 20% of breast cancers that are HER2+, as an essential medicine for early stage breast cancer and metastatic cancers. There is clear benefit in disease-free and overall survival for women on trastuzumab. Here, we catalogue the most recent data on effectiveness from over 12,000 women studied and highlight the most recent safety and regulatory information. We note, as the special Expert Committee meeting in 2002 for HIV/AIDS noted, that the addition of critical medicines to the WHO Essential Medicines List that appear unaffordable can, in reality, serve as a vital lever in expanding access to these medicines and in making them affordable. This would include but not be limited to actions by governments to overcome patent barriers -- actions that were used to expand access to drugs for HIV/AIDS -- and to measures that address the need for efficient regulatory pathways for approvals of less expensive biosimiliar/biogeneric products. We further note the proliferation of chronic care centers in resource-poor settings that include testing, follow-up and provisions for chemotherapy, as well as innovations in treatment delivery that could support and enable the delivery of trastuzumab to patients worldwide.

2. Name of the focal point in WHO submitting or supporting the application

N/A

3. Name of the organization(s) consulted and/or supporting the application

The following organizations are supporting this application:
Knowledge Ecology International (KEI)
University of California, San Francisco
Universities Allied for Essential Medicines (UAEM)
Third World Network (TWN)

4. International Nonproprietary Name (INN, generic name) of the medicine

Trastuzumab

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Trastuzumab is currently distributed in a variety of vial sizes: 60mg, 150 mg, 400mg, 440 mg as a powder for solution, administered as intravenous infusion

6. International availability - sources, if possible manufacturers and trade names

Trastuzumab is sold internationally under the brand name Herceptin, a product of Genentech/F. Hoffmann-La Roche Ltd., as well as through arrangements with other companies.

Reports of several firms involved in the development and testing of biosimilar versions of trastuzumab [48-50] indicate that cheaper alternatives to Roche's product, Herceptin may enter some international markets as early as 2013.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance

8.1 Global burden of cancer

Cancer kills more people every year around the globe than HIV, tuberculosis and malaria combined.[1] Cancer accounts for one out of eight deaths annually and is the second leading cause of death in the world after heart disease. Unfortunately, information about the epidemiology of cancer in the world is not complete - incidence data for cancer is estimated from cancer registry data that covers 16% of the world population: 64% of developed countries and 5% of developing countries.[2] Estimated incidence and mortality for various cancers is reported by the International Agency for Research on Cancer through their Globocan project. The latest estimates are from 2008.[3]

8.2 Breast cancer

Globally, breast cancer is the most common cancer for women in both developing and developed countries, and the leading cause of cancer death for women.[4] One in ten cancers diagnosed annually worldwide is a cancer of the female breast, and one in ten women will develop breast cancer in her lifetime. Globocan data reveal that 1.38 million women around the globe were diagnosed with breast cancer in 2008; 458,000 women died because of breast cancer in that year, and the five-year prevalence of breast cancer was 5.19 million women. By 2030, the annual incidence is predicted to increase to as high as 2.7 million.[2] [3]

A separate estimate for breast cancer incidence has been made by the Institute of Health Metrics and Evaluation, using a Gaussian regression model. This group estimated that, in 2010, there were 1.64 million women diagnosed with breast cancer worldwide in 2010. [10]

8.3 HER2 receptor as a target for breast cancer therapy

17-30% of breast cancers have a HER2-positive phenotype, so-called because these tumors over-express a tyrosine kinase-linked receptor, called the human epidermal growth factor 2 receptor, or HER2 receptor (previously called ERB-B2/Her2neu). HER2-positive tumors are more aggressive and less responsive to standard chemotherapy than HER2-negative tumors. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. [42]

Currently, each year, at least 276,000 women worldwide are newly diagnosed with HER2-positive breast cancer (1.38 million * 20%) and in the year 2030, an estimated 540,000 women will be diagnosed with HER2-positive breast cancer (2.7 million * 20%). Surgically biopsied or resected breast tumors are tested for HER2 positivity using an immunohistochemical (IHC) stain and, if inconclusive, confirmed using a Fluorescent In-situ Hybridization (FISH) test. High levels of HER2 expression predict tumors that will respond to agents that target the receptor. HER2 status also predicts whether a tumor will respond to or have resistance to certain types of cancer chemotherapy and endocrine therapies.[5] Several expert panels, including the U.S. National Comprehensive Cancer Network and the International Consensus Panel on the Treatment of Early Breast Cancer, recommend that tumors from all patients with newly diagnosed breast cancer be tested for HER2 over-expression.[4]

8.4 Trastuzumab, an antibody targeting HER2 receptor

Trastuzumab is a drug that targets the extracellular domain of HER2. Trastuzumab is a recombinant humanised IgG1 monoclonal antibody that binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. [51]

Following surgery for early stage (non-metastatic), HER2-positive breast cancer, trastuzumab is indicated as adjuvant therapy for 12 months, concurrently and following chemotherapy. Clinical trials have demonstrated an improvement in both disease free survival and overall survival for women with early stage and locally advanced breast cancer

(those without metastatic disease). [6] While trastuzumab is currently commercially available only in an IV formulation, a 2012 clinical trial suggests that a subcutaneous formulation of trastuzumab may be equally effective as compared to IV, which would greatly improve ease of administration, particularly in certain low resource settings where there is a shortage of trained clinical staff, space and time for IV infusions.[7,52]

8.5 Other uses for trastuzumab

Trastuzumab is indicated for use, as per the manufacturer (Genentech, Inc), not only for HER2-positive early stage breast cancer, but also for HER2-positive metastatic breast cancer and for HER2-positive gastric/gastroeosphageal cancer.[11] Clinical trials will soon be in development to test whether HER2 is a potential target in ovarian cancer, as well. [8]

Trastuzumab is approved for HER2-positive metastatic breast cancer as first-line treatment, concurrently with Paclitaxel (US) or Docetaxel (Europe) chemotherapy. It is also approved as single agent therapy after one or more chemotherapy regimens for HER2-positive metastatic breast cancer have failed. Over the past 30 years, survival for metastatic breast cancer has improved in one subset of patients -- those who have tumors that are hormone (estrogen and progesterone) receptor-negative, HER2+, and have been treated with trastuzumab.[12]

One of the most dramatic set of results from trastuzumab has been as neo-adjuvant (pre-surgical) therapy for locally advanced breast cancer.[7] In a U.S. clinical trial, 221 patients with tumor ≥3 cm received neoadjuvant chemotherapy consisting of doxorubicin plus cyclophosphamide followed by paclitaxel [9]. Of 66 patients with HER2-positive disease, 20 received neoadjuvant trastuzumab after it became available for use in the adjuvant setting. The main results were as follows:

1. The pathologic complete response (pCR) rate following neoadjuvant chemotherapy alone was 39 percent (18 of 46 patients) for patients with HER2-positive disease. In contrast, the pCR rate was 18 percent for those with HER2-negative breast cancers (26 of 144 patients).
2. Among HER2-positive patients treated with neoadjuvant chemotherapy plus trastuzumab, the pCR rate was 60 percent (12 of 20).[5]

Although it is rare, not all women with tumors expressing high levels HER2 will respond to trastuzumab, for unclear reasons. [13] Notwithstanding, it is interesting to note that there have been several cases of women whose tumors have responded to trastuzumab despite being HER2-negative.[14]

Trastuzumab is also being tested in combination with other therapies in the adjuvant and metastatic setting, including lonafarnib, a farnesyl transferase inhibitor, in order to simultaneously inhibit multiple pathways for breast tumor cell proliferation. [15]

8.6 Extending the EML to include targeted anti-cancer therapy

Trastuzumab is one of many medications in a large, diverse class of targeted, anti-cancer therapies that are specific to receptors on the surface of and inside of cancer cells. This group includes large molecule antibodies such as trastuzumab, bevacizumab, cetuximab and rituximab, as well as small molecules such as the tyrosine kinase inhibitors - lapatinib, imatinib, sorafenib, and erlotinib. The medications in this class have transformed the way cancer is treated and have extended the lives of countless patients.

9. Treatment details

9.1 Localised breast cancer

For localised breast cancer, treatment may be administered in either three week or one week regimes. The duration of treatment is one year.

A. Three weekly regimen

After completion of neoadjuvant therapy and surgery or at least 4 cycles of adjuvant chemotherapy.

Loading dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Total duration of treatment: 1 year

B. Weekly regimen

Following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide adjuvant chemotherapy, with either

· paclitaxel (weekly or 3-weekly schedule) for 12 weeks, then as a single agent for a further 40 weeks; or

· docetaxel or docetaxel and carboplatin (3-weekly schedule for 6 cycles (18 weeks), then as a single agent

Loading dose: an initial dose of 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent doses: 1 week after the loading dose administer 2 mg/kg body weight at weekly intervals. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

9.2 Locally advanced breast cancer

With neoadjuvant doxorubicin and paclitaxel, until surgery and continued as a single agent following surgery, for a total of 1 year.

Loading dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

9.3 Metastatic Breast Cancer

Loading Dose: The recommended initial loading dose is trastuzumab 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent Doses: The recommended weekly dose of trastuzumab is 2 mg/kg body weight given at weekly intervals. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

In clinical trials, patients with metastatic breast cancer were treated with trastuzumab until progression of disease. For patients who respond well to trastuzumab, the drug should be taken as long it continues to control the progression of the disease. Because of the current high cost of the drug, some patients are discouraged by insurance/reimbursement entities from using trastuzumab for extended periods, but at a lower price, these price related restrictions are expected to shrink or disappear.

10. Summary of comparative effectiveness in a variety of clinical settings:

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving trastuzumab in at least one arm were searched on the Database of Abstracts of Reviews of Effectiveness [16]. Additional searches for relevant reviews were undertaken of Clinical Evidence (CE) [17] and the Cochrane Database of Systematic Reviews. Medline was also searched for any relevant RCTs published after the cutoff dates of the identified reviews.In addition, the Cochrane Database was searched for relevant HTA reports and economic evaluations.

10.2 Summary of available data

10.2.1 Early and Locally Advanced Breast Cancer

In a systematic review published in 2012, *Moja et al* [18] assessed data from published and unpublished RCTs comparing the efficacy and safety of trastuzumab alone, or in combination with chemotherapy, vs. no treatment, vs. standard chemotherapy alone, in women with HER2-positive early breast cancer, including women with locally advanced breast cancer. The authors searched the Cochrane Breast Cancer Group's (CBCGs) Specialised Trials Register, and used the search strategy developed by the CBCG to search for RCTs in CENTRAL, MEDLINE, EMBASE, BIOSIS, TOXNET, and the WHO ICTRP search portal (up to February 2010). The review included a total of eight studies involving 11,991 patients.

The eight included RCTs evaluated the efficacy of trastuzumab and other comparators in patients with early and locally advanced breast cancer [19-26] (B31; BCIRG006; Buzdar; FinHer; HERA; N9831; NOAH; PACS-04). Seven RCTs [19,21-26] were published in full

in peer reviewed journals (some with meeting updates); at the time the review was undertaken, data from the 8th trial were available only as meeting abstracts or presentations. For some trials, additional unpublished data were obtained from investigators, regulatory agency reports or trial registries.

In the eight RCTs, 11,991 women were randomised to the following treatment groups: 7,020 women to a trastuzumab-containing arm and 4,971 women to a treatment without trastuzumab. age range (22-80 years, median 49 years). The trials recruited patient populations with varying risk profiles but all trials excluded patients with metastatic breast cancer.

All included patients had local (axillary) node-positive breast cancer or high risk node-negative disease on the basis of the size of the primary tumour and were HER2-positive. Four trials included patients both with (node-positive) and without (node-negative) pathological axillary lymph nodes [20,22-24). To be eligible, node-negative patients in these studies had to have a primary tumour bigger than 2 cm [22,24] or 1 cm [23] in diameter. The BCIRG006 trial [20] did not specify the criteria for defining patients with node-negative disease at high risk. The B31 and PACS-04 trials [19,26] included patients with positive axillary metastases. The two neoadjuvant trials, Buzdar and NOAH [20,24], included patients with T3N1, T4, any T plus N2 or N3, or any T plus involvement of ipsilateral supraclavicular nodes (NOAH), or patients with clinical stage II-IIIA (Buzdar).

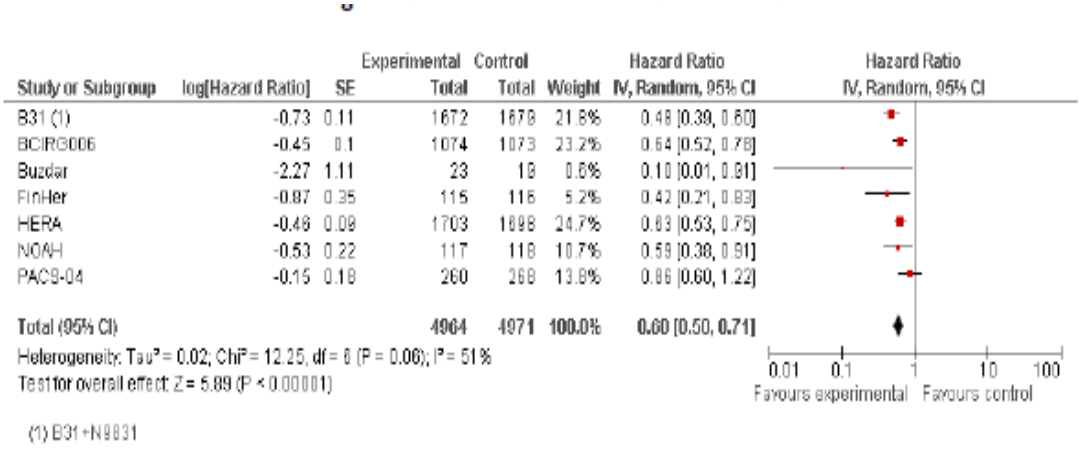
Surgical resection of the primary tumour was required in all but two trials [21,25] which considered a neoadjuvant therapeutic setting. Patients with cardiovascular disease of any grade were excluded from all trials. Both premenopausal and postmenopausal women were eligible in all trials.

The combined HRs for overall survival (OS) and disease-free survival (DFS) significantly favoured the trastuzumab-containing regimens (HR 0.66; 95% CI 0.57 - 0.77, $P < 0.00001$; and HR 0.60; 95% CI 0.50 - 0.71, $P < 0.00001$, respectively). In the systematic review by Moja et al, the results are presented only as hazard ratios.

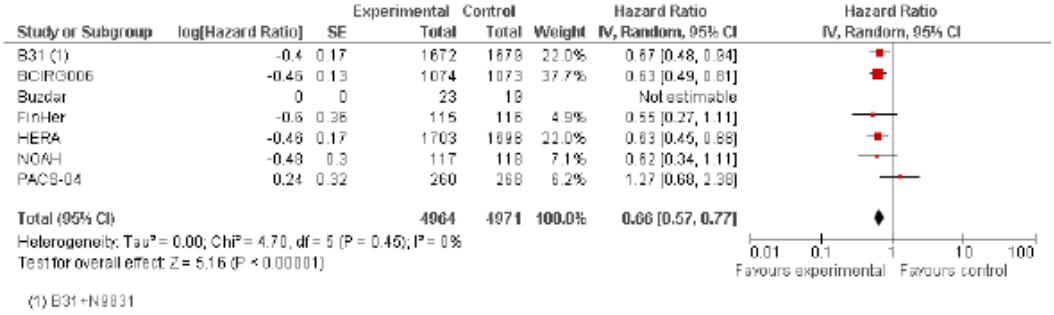
In the B-31 and N9831 trials less than 2% of subjects were considered ineligible at baseline for any reason.

The Buzdar trial excluded patients with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45%; Finher excluded subjects with cardiac disease (including cardiac failure of any degree, arrhythmia requiring regular medication, and myocardial infarction within the previous 12 months); HERA and NOAH excluded patients with LVEF<55%. However the numbers of patients excluded from these trials for cardiac or any other reasons were not stated.

Overall Survival – All Studies [ref Moja et al, 2010]



Disease- free Survival – All Studies [ref Moja et al, 2010]



The authors concluded that trastuzumab significantly improved OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increased the risk of CHF and LVEF decline (See Section 11 for further discussion of this). They noted that *studies that administered trastuzumab concurrently or sequentially did not differ significantly in efficacy*, and that while shorter duration of therapy may reduce cardiotoxicity and maintain efficacy, there was insufficient evidence to conclude this due to small numbers of patients in the relevant trials.

10.2.2 Efficacy of trastuzumab with adjuvant chemotherapy

Yin et al [27] reviewed the use of trastuzumab in the adjuvant treatment of HER2-positive early breast cancer in which they identified six eligible studies assessing the benefits of concurrent or sequential trastuzumab with adjuvant chemotherapy for early breast cancer patients with HER2-positive tumors. The analysis demonstrated that patients with

HER2-positive breast cancer derive benefit in terms of disease-free survival, overall survival, loco-regional recurrence and distant recurrence (all $p < 0.001$) from the addition of trastuzumab to adjuvant chemotherapy, but have a higher rate of CNS recurrence ($p = 0.018$). While concomitant use of trastuzumab significantly lowered the hazard ratio for mortality, yet was associated with a higher incidence of CNS recurrence ($p = 0.010$). Notwithstanding, there was no statistically significant difference in overall survival or CNS metastasis between the sequential therapy and observation arms. The authors concluded that the meta analysis confirmed the efficacy of trastuzumab in the adjuvant setting and provided indirect support to corroborate the superiority of concurrent vs. sequential use of trastuzumab. [27]

10.3 Metastatic Disease

Metastatic breast cancer refers to disease that has spread beyond the breast and regional lymph nodes. Treatment for metastatic breast cancer is focused on symptom management and long term survival. A Cochrane review of RCTs entitled *'Trastuzumab-containing regimens for metastatic breast cancer'* is currently in progress.[28] A systematic review entitled *'The efficacy of HER2-targeted agents in metastatic breast cancer: a meta-analysis'* was published in 2010 by a group at the University of New South Wales.[29] In this review, Harris et al evaluated RCTs in which various chemotherapy drugs were combined with one of two different HER2-targeted drugs, trastuzumab or lapatinib (an EGFR and HER2 targeted tyrosine kinase inhibitor).

The combined analysis of five of these RCTs demonstrates that the addition of HER2-targeted therapies to standard chemotherapy results in a 22% increase in overall survival, although the median follow up is not specified (range 15.6 months-30 months, and time not specified for 2 of the trials). [29]

This is similar to the pivotal trial done in 2001, in which the addition of trastuzumab to chemotherapy reduced the relative risk of death by 20% at a median follow up of 30 months. [30]

11. Summary of comparative evidence on safety

11.1 Cardiomyopathy

The most well known adverse effect from trastuzumab is a reduction in left ventricular ejection fraction (LVEF), which may lead to clinically significant heart failure. This adverse effect was noted in the original clinical trials in patients with advanced disease. [31,32] The pathophysiology of the reduction in LVEF is tied directly to trastuzumab exposure, but is also thought to be exacerbated by prior or concomitant exposure to cardiotoxic chemotherapy such as anthracyclines. Individual studies and meta-analysis have been undertaken to assess risk-benefit analysis, especially in patients with low-risk disease. [6,32-33]

The aforementioned 2012 Cochrane review investigated cardiotoxicity of trastuzumab in early breast cancer; it included eight randomized controlled trials (RCTs), with 11,991 women. [18] 7,020 women were exposed to a trastuzumab-containing regimen and 4,971 women to a treatment without trastuzumab. Though the age range was from 22 to 80 years the median age was 49. The combined hazard ratios for overall survival (OS) and disease-free survival (DFS) were 0.66 (95% confidence interval (CI) 0.57 to 0.77, P < 0.00001) and 0.60 (95% CI 0.50 to 0.71, P < 0.00001), respectively, statistically in favor of the trastuzumab-containing regimens. The relative risk of developing congestive heart failure (CHF), and LVEF decline was (CHF) 5.11 (90% CI 3.00 to 8.72, P < 0.00001) and (LVEF) 1.83 (90% CI 1.36 to 2.47, P = 0.0008). However, the absolute numbers were 135 cases (2.5%) of CHF out of 5471 patients in the trastuzumab group and 20 cases (0.4%) out of 4810 in the control group.

An earlier pooled analysis in 2011 looked at trastuzumab exposure in both early and advanced breast cancer patients. [32] There were a total of 11,882 patients from 10 RCTs (there was a significant overlap of RCT's between both meta-analysis).

The incidences of LVEF decrease, and congestive heart failure (CHF) were 7.5% (95% CI 4.2-13.1) and 1.9% (95% CI 1.0-3.8), respectively, with trastuzumab exposure. The risk of CHF, and LVEF decline with trastuzumab were (CHF): RR 4.05 (95% CI 2.49-6.58; p < 0.00001) and (LVEF): RR 2.13 (95% CI 1.31-3.49 P= 0.003). In a sub-group analysis of available data, the increased risk of CHF with trastuzumab was only statistically significant in patients on anthracycline-based chemotherapy; (anthracycline-based chemotherapy) RR 4.27 (95% CI 2.75-6.61, p < 0.00001), (non-anthracycline chemotherapy) RR 2.42 (95% CI 0.36-16.19, p = 0.36). Despite the increased incidence of CHF, there was no increase in cardiac-related death with trastuzumab.

CHF and LVEF decline with trastuzumab is thought to be reversible by stopping the medication and with routine management of CHF in symptomatic patients. [31,35] A 2012 study with seven-year follow up of 1830 patients, 944 of whom received trastuzumab, did not show any ongoing clinically significant cardiac dysfunction compared to control. [33]

LVEF monitoring with echocardiogram or MUGA (Multi Gated Acquisition) scan is recommended by the manufacturer at various intervals: prior to initiating therapy, at 3 month intervals while on therapy, at the end of therapy, and every 6 months for 2 years after completion of use as adjuvant chemotherapy. [31,34-35] The manufacturer also recommends holding the medication for 4 -8 weeks if there is a 16% absolute decrease in LVEF from pre-treatment values, or if there is an absolute decrease in LVEF of 10% from pretreatment values and the value falls below institutional limits of normal. Re-challenge of trastuzumab with close LVEF monitoring has been reported in patients who have had recovery in cardiac function. [31,35]

Precautions and detailed analysis of individual patients' risk and benefit is encouraged for patients with risk factors for cardiac dysfunction including older age, history of coronary

artery disease, uncontrolled hypertension, hyperlipidemia and other cardiomyopathies. [31,35]

11.2 Infusion reactions

Infusion reactions can occur with chemotherapy and biologic agent infusions. They range from mild, with chills and nausea, to severe/ life threatening with respiratory and cardiovascular collapse. One of the early studies on trastuzumab in metastatic breast cancer patients reported rates of mild-moderate transfusion reactions ranging between 14 to 25%, with chills occurring most frequently. [36] Early post-marketing surveillance reported incidence of severe transfusion reaction of 74 out of a total exposure of 25, 000 patients. The severe reactions tended to occur during the initial infusion. 65 of the patients with severe reactions had favorable outcomes with supportive management while there were nine deaths. These reactions are idiosyncratic. Close monitoring is recommended with initial doses; decreasing the infusion rate and administering subsequent doses with pre-medications (analgesia, anti-histamine, anti-inflammatory, or anti-emetic medications) is usually sufficient for mild-moderate infusion reactions. Despite evidence that re-challenge with premedication is often successful in severe reactions, assessment of risk and benefit on an individual basis is recommended for these patients. [37]

11.3 Hematologic side effects

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. [38]

11.4 Other side effects

Pulmonary toxicity has also been described, with the incidence being idiosyncratic. The type of pulmonary pathology seen is variable, including idiopathic hypoxia, pneumonitis, hypersensitivity reactions, non-cardiogenic edema, ARDS and pulmonary fibrosis. [31,39] The exact incidences of these disorders are unknown but thought to be rare, with very rare associated mortality. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common. Asthenia, chest pain, and renal or liver disorders have also been reported less frequently. [38]

11.5 Identification of variation in safety due to health systems and patient factors

The most clinically significant adverse side effect is cardiomyopathy as discussed in 11.1. The recommended monitoring and screening intervals with cardiac imaging are described above; echocardiogram or nuclear cardiac scans are the common modalities. [35] Frequent cardiac imaging adds to the overall cost of using trastuzumab. Advanced cancer care world-wide is generally delivered in integrated health facilities where access to routine blood work and imaging is available. In the developing world, cancer centers of excellence already with capacity to deliver cytotoxic chemotherapy would be capable of administering

and monitoring infusions. HER2 testing is performed to identify appropriate candidates for HER2-targeted therapy with trastuzumab. and is further discussed in section 8.3.

11.6 Summary of safety against comparators

Few medications target the HER2 receptor, such that few comparative studies have been performed. There are now several targets along the EGFR HER2 signal transduction pathways for which inhibitory molecules and antagonizing antibodies have been developed. The two agents that are most developed are lapatinib and pertuzumab. Both medications have been approved by the United States Food and Drug Administration for breast cancer. [39,40,42]

Comparison with lapatinib

Lapatinib is a reversible, small molecule tyrosine kinase inhibitor that targets the HER2 intracellular domain (JCO 2012) It is currently indicated in HER2-positive advanced breast cancer (in combination with capecitabine) in patients who have progressed while on trastuzumab combination therapy. The significant side-effects attributed to lapatinib are diarrhea and dermatologic manifestations including hand-foot syndrome and a variety of rashes; the incidence in the pivotal studies were 65% and 53% respectively. [39] Rare toxicities include pulmonary toxicity, hepatotoxicity and QTc prolongation. [40] It is yet unclear how lapatinib compares to trastuzumab alone in terms of LVEF reduction. [39, 41] In a study of HER2-positive patients who progressed on prior trastuzumab-based combination therapies, lapatinib in combination with trastuzumab improved overall survival when compared to lapatinib alone. [42]. However, of a total 291 patients, 26% had serious adverse events in the combination arm, with 14% in the lapatinib only arm. Ten events in the combination arm and three in the monotherapy arm met the criteria for serious cardiac events.

Comparison with pertuzumab

Pertuzumab is a monoclonal antibody that binds subdomain II of the HER2 extracellular domain and prevents HER2 homo- and heterodimerization with other HER-family receptors. It is approved for use in the US for patients with HER2-positive breast cancer, in combination with chemotherapy plus trastuzumab. thought to be a less potent inhibitor than trastuzumab but it potentiates trastuzumab inhibition. [42-44]

The pivotal study for pertuzumab showed increased incidence of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin with the pertuzumab addition arm compared with the control (trastuzumab plus docetaxel) arm. It also showed increase in median progression-free survival to 18.5 months in the pertuzumab group compared to 12.4 months in the control group. [53] Data for LVEF dysfunction in pertuzumab is not very robust since it is a new agent. However, a pooled analysis comparing single agent pertuzumab to pertuzumab in combination with non-anthracycline chemotherapy or trastuzumab did not show significant differences in LVEF or symptomatic heart failure among the groups. [54] Recommendations for LVEF monitoring are similar for pertuzumab as they are fortrastuzumab.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

12.1 Range of costs for trastuzumab

The current cost of trastuzumab from Roche is high, and it is important to keep in mind that the petition is based upon the possibility of obtaining lower cost biosimiliar products.

A list of recent prices for trastuzumab in several countries is available in a Google Doc spreadsheet, available at: http://goo.gl/ERyYW. Pricing data were obtained from responses to an online survey well as by searching publicly available sources. The drug is typically sold in 150 milligram or 440 milligram vials, but in some countries is also available in 60 milligram vials. In all cases, the quoted prices are for products that are either sold directly by Roche or supplied through arrangements with other companies.

Based upon the prices in the survey (expressed in USD) the cost of trastuzumab from Roche ranges from a low of $3,035.95 per gram in Pakistan to a high of more than $10,000 per gram in Brazil and Oman. The price on the US Federal Supply Schedule is $6,266.23 per gram, and the prices in most countries are between $5,000 and $9,000 per gram. Even in India, where Roche has implemented price cuts and launched lower priced versions of trastuzumab (Herclon, Biceltis), trastuzumab from Roche is expensive.

Apart from the cost per vial, the cost of treatment for any given patient depends upon the patient's weight, the ability of the patient to only pay for the amount of the drug needed (rather than a whole vial) and the treatment regimen used. Studies of the cost of trastuzumab make different assumptions regarding average or median patient weight, typically in the range of 58 to 68 kilos. In Australia, an information sheet for medicare reported that 70 percent of herceptin patients with metastatic disease were under 75 kilos, and 30 percent were over 75 kilos.

Late stage metastatic breast cancer, Medicare Australia

Month Ending	Patients Under 75 Kg	Patients over 75 Kg	Total number of Patients
June 2011	3040	1269	4309

Source: http://www.medicareaustralia.gov.au/provider/patients/late-breast-cancer.jsp

The dosing and mg/kg is discussed in Section 9. Per patient use will depend upon several factors, including but not limited to the patient weight and the ability to efficiently share vials, which come in limited sizes. The use of 150 mg per week for 52 weeks is 7.8 grams/year. In one 2006-2007 NICE evaluation, a typical patient was assumed to have used 150 mg x 56.2 vials of trastuzumab, or 8.43 grams per year.

For a patient using 150 milligrams week, the annual cost of buying the drug from Roche will be anywhere from just over $23,000 in India and Pakistan, to $45,710 in South Africa, more than $73,000 in Lebanon and $78,000 in Brazil.

It is unlikely that trastuzumab will be widely used in developing countries, despite its medical benefits, unless it is possible to obtain lower cost versions.

It is the view of the petitioners that it is possible to obtain trastuzumab at far lower prices than are currently available in any country. However, because trastuzumab is a monoclonal antibody, there are challenges to obtaining low priced versions. These challenges include the trade secrets associated with the manufacture of the drug, patents and test data protection, the difficult and in many countries undeveloped regulatory pathway for biosimilar products, and because of market entry barriers, the potential lack of competition among manufacturers supplying the drug.

Before addressing the challenges in obtaining low cost versions, it is useful to consider differences between the prices per gram for trastuzumab from Roche and some other relevant products, as suggestive of how much prices could fall if buyers can overcome intellectual property and regulatory barriers to competition, and engage in effective procurement strategies with manufacturers.

For pharmaceutical drugs purchased in large quantities for HIV, the prices per gram of active ingredient are far lower. For example, in the table below, for both newer and older HIV products, manufactured by both Indian and US manufacturers, the prices range from $.51 to $2.38 per gram of active ingredient.

Product	dose of active ingredient, mg	price per tab or cap	price per gram in USD
3TC, d4T, NVP	480	.83	$1.73
atazanavir/ritonavir ATV/r	400	.833	$2.08
lopinavir LPV/r	250	.252	$1.01
raltegravir RAL, sold by Merck	400	.95	$2.38
tenofovir	300	.162	$.5425
tenofovir/emtricitabine	500	.255	$.51

Among cancer drug prices available from MSH, prices vary considerably, but for several where sufficient competition and demand exists, prices range from $6.40 to $275 per gram. Note that cancer drugs often do not benefit from the types of procurement efficiencies that exist for several HIV drugs.

The current Roche prices range from $3,000 to $9,000 per gram, but one possible supplier of trastuzumab suggested the drug could be manufactured for $31 per gram, or $242 per year, roughly one percent of the lowest Roche price.[55]

In evaluating the placement of trastuzumab on the list of essential medicines, WHO should deal explicitly with the huge differences between the prices charged by Roche and the much lower prices that are possible from generic suppliers.

WHO has several possible ways of dealing with the pricing issue. WHO could take the Roche prices as a state of nature and reject the application on the grounds that trastuzumab is not cost effective in a resource poor setting. Or, WHO could say that trastuzumab is medically important enough to be included in the list if the country can obtain the drug at an affordable price. WHO could also identify the measures that will be necessary to expand access to the drug at affordable prices, including the measures necessary to overcome intellectual property barriers, a biosimilar pathway for drug registration, including a WHO prequalification process for trastuzumab, and also the efficient procurement strategies that have proved to be useful in bringing down prices for HIV drugs.

12.2 Comparative cost-effectiveness

Comparative cost-effectiveness is typically presented as range of cost per natural unit of outcome (e.g. cost per cure, cost per month of treatment, cost per clinical event prevented) or, if possible and relevant, cost per death averted or cost per quality adjusted life year gained.

Because the medical evidence is strong that trastuzumab extends lives and often significantly so, the major barrier to its use has been the high cost of the product from Roche. An additional issue in the cost effectiveness studies is the cost and availability of diagnostic technologies, including in particular the costs of the Fluorescent in-situ hybridization (FISH) test to more accurately identify the patients that will benefit from trastuzumab.[45]

In high income countries, trastuzumab has received a number of positive cost-effectiveness assessments for both first line treatment and as a treatment for metastatic disease. The challenge for WHO is to evaluate cost effectiveness in countries with incomes lower than the UK, France, Canada or the United States.

In a 2009 study, L Ferrusi Ilia et al. [45] published a systematic review of economic analyses of trastuzumab therapy. They found mixed reviews of the cost effectiveness of treatment for metastatic disease, and more favorable results for early-stage disease.

> A total of eight out of the 10 analyses of trastuzumab in early-stage disease concluded that it was a cost-effective treatment option vis a vis the identified comparators, . .. We found that cost–effectiveness estimates in early-stage disease were more favorable than those in the metastatic breast cancer setting. Some variation was noted across geographical regions; European estimates

> ranged from $6,783 per life year gained (LYG) to US$65,250/QALY, North American estimates ranged from US$20,065 to US$43,330/QALY, while all other regions ranged from US$14,083/QALY to US$23,309/LYG. When comparing within outcome type, the ranges between estimates were more similar: US$13,361–65,250/QALY and US$6,783–51,976/LYG. Some of this variation can be explained by the choice of trastuzumab regimen. Estimates for 52-week therapy ranged from US$13,361–65,250/QALY, while estimates for the 9-week regimen were US$6,783/LYG to US$14,083/QALY.

In a 2009 study in the *American Journal of Clinical Oncology*, C. Perez-Ellis et al evaluated the cost-effectiveness of trastuzumab in metastatic breast cancer (MBC) patients in France[46].

> We carried out the first cost-effectiveness study for trastuzumab in metastatic breast cancer (MBC) patients, in France, that is based on observed resource use and outcomes in clinical practice. . . In the trastuzumab group, median overall survival was significantly higher (37 months vs. 19 months in the non-trastuzumab group, P = 0.001) but total treatment costs were 3 times higher (€ 39,608 vs. € 12,795). The cost per additional life-year saved by trastuzumab treatment was estimated to be € 27,492 . . . Our data suggest that despite its high unit price, trastuzumab should be considered cost-effective in MBC patients to the extent that its incremental cost per life-year saved remains lower than gross domestic product per capita in countries like France.

In a 2010 evaluation by NICE that recommended "trastuzumab for the treatment of HER2-positive metastatic gastric cancer," the following observations were made:

> NICE technology appraisal guidance 208 [47]
>
> 2.4 The net price of a 150-mg vial of trastuzumab is £407.40 (excluding VAT; 'British national formulary' [BNF] edition 59). For a patient weighing 62 kg, four vials are required for the first loading dose and three vials for each subsequent dose. Assuming that excess trastuzumab is wasted, the drug cost of eight infusions of trastuzumab (the median number of infusions in the regulatory trial) is £10,185. Costs may vary in different settings because of negotiated procurement discounts.
>
> 4.17 The Committee noted the manufacturer's assumption that sharing vials between patients to minimise wastage would occur in 80% of centres. It considered that this might be an overestimate and that in some centres, particularly smaller centres, sharing vials may not be possible, and therefore there was likely to be large variation in vial sharing. The Committee concluded that there was not enough evidence to estimate the proportion of centres that would vial share in clinical practice, but that 80% could be an overestimate.

In all of these studies, the very high prices for trastuzumab from Roche were quite important, and it is a measure of the medical benefits of the drug that despite these high prices, many high income countries included the drug on national schedules for reimbursement for both early-stage and metastatic breast cancer.

In evaluating the cost effectiveness of trastuzumab, we ask that WHO consider at what price trastuzumab becomes cost effective, for countries at different stages of development and income. Clearly a price of $3,000 to $10,000 per gram will discourage many developing countries from buying the drug, just as the high price of branded HIV drugs were a disincentive for use in 2000. But if trastuzumab can be obtained for more reasonable prices, including cases where governments grant compulsory licenses on patents and grant regulatory approval to biosimilar products, the cost effectiveness of the drug changes. This is not an abstract issue -- the lives of many women with breast cancer will depend upon the actions that WHO and others take to expand access to trastuzumab. For the many patients for whom the drug is medically essential the recognition by the WHO that trastuzumab is an essential medicine should contribute to and be part of larger efforts to make trastuzumab more affordable and truly accessible.

13. Summary of regulatory status of the medicine

Trastuzumab is approved for use in various jurisdictions as follows:

EU (EMA)

Trastuzumab is licensed in the EU for the treatment of:

- **HER2 positive early breast cancer** following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- **HER2 positive metastatic breast cancer:**

  i. as monotherapy for patients who have received at least two chemotherapy regimens including, where appropriate, an anthracycline and a taxane. Hormone receptor positive patients must also have failed hormonal therapy, where appropriate.

  ii. in combination with paclitaxel for patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

  iii. in combination with docetaxel for patients who have not received chemotherapy for their metastatic disease.

  iv. in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive HER2 positive tumours, not previously treated with trastuzumab.

US (FDA)

Adjuvant Breast Cancer Trastuzumab is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • with docetaxel and carboplatin • as a single agent following multi-modality anthracycline based therapy.

Metastatic Breast Cancer Herceptin is indicated: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Australia (TGA)

Locally Advanced Breast Cancer - trastuzumab is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab.

Localised Breast Cancer - trastuzumab is indicated for the treatment of patients with HER2 positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Metastatic Breast Cancer - trastuzumab is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

• As monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease

• In combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or

• In combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Herceptin (trade name of trastuzumab) is reported to be currently registered for sale in the following countries (Source: *Martindale: The Complete Drug Reference. Sweetman, Sean. Thirty-seventh edition***)**

Argentina	Armenia	Australia
Austria	Bahrain	Bangladesh
Belgium	Bolivia	Bosnia & Herzegovina
Brazil	Canada	Chile
China	Colombia	Croatia
Cuba	Cyprus	Czech Republic
Denmark	Ecuador	Egypt
Finland	France	Georgia
Germany	Greece	Hong Kong
Hungary	Iceland	Indonesia
Iran	Iraq	Ireland
Israel	Italy	Jamaica
Japan	Kazakhstan	Kuwait
Latvia	Lebanon	Lithuania
Luxembourg	Mexico	Moldova
Netherlands	New Zealand	Norway
Oman	Paraguay	Philippines

Poland	Portugal	Romania
Russian Federation	Saudi Arabia	Serbia
Singapore	Slovakia	Slovenia
South Africa	South Korea	Spain
Sweden	Switzerland	Syria
Taiwan	Thailand	Trinidad & Tobago
Tunisia	Turkey	United Arab Emirates
United Kingdom	United States	Uruguay
Uzbekistan	Venezuela	Yemen

14. Availability of pharmacopoeial standards

None specific to trastuzumab.

The British Pharmacopoeia has a General Notice on monoclonal antibodies (Monoclonal Antibodies for Human Use) taken from the European Pharmacopoeia (Ph. Eur. monograph 2031).

The United States Pharmacopoeia (USP) in 2011:

Under the guidance of the USP General Chapters—Biological Analysis Expert Committee, two new chapters are being developed by the USP Recombinant Therapeutic Monoclonal Antibodies Expert Panel: General Chapter *Critical Quality Attributes of Recombinant Therapeutic Monoclonal Antibodies* <129>, and General Information Chapter *Recombinant Therapeutic Monoclonal Antibodie*s <1260>.

General Chapter <129> is being developed as a class chapter with relevance to all MAbs. As a sub-1000 chapter in *USP–NF*, this chapter will be mandatory and will provide a minimum quality standard to which all monoclonal antibody manufacturing subject to USP standards must adhere.

General Chapter *Recombinant Therapeutic Monoclonal Antibodies* <1260> is a general information chapter that will provide guidance on various aspects of monoclonal antibody structures, functions, manufacturing and controls. This chapter is less prescriptive than a sub-1000 chapter in *USP–NF* and is considered informational by USP.

15. Proposed (new/adapted) text for the WHO Model Formulary

Trastuzumab
Powder for injection: 60 mg; 150 mg; 400 mg; 440 mg vials
Trastuzumab is used for the treatment of HER2 positive breast cancer.

Uses

1. In HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
2. In HER2 positive locally advanced breast cancer in combination with neoadjuvant chemo-therapy followed by adjuvant trastuzumab.
3. In HER2 positive metastatic breast cancer:
   i. as monotherapy for patients who have one or more chemotherapy regimens for their metastatic disease
   ii. in combination with taxanes for patients who have not received chemotherapy for their metastatic disease.
   iii. in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive HER2 positive tumours, not previously treated with trastuzumab.

Contraindications: Trastuzumab is contraindicated in patients with known hypersensitivity to trastuzumab, chinese hamster ovary cell proteins or to any other component of the product. In the treatment of localised or locally advanced breast cancer, trastuzumab is contraindicated in patients with a left ventricular ejection fraction of less than 45% and those with symptomatic heart failure.

Precautions:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension
- Patients with New York Heart Association (NYHA) class ≥ ii disease i.e. Cardiac disease with limitation of physical activity.

Interactions: Appendix 1.

Dose: Not to be administered as an intravenous push or bolus.

Localised breast cancer

A. Three weekly regimen

Following surgery and completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy
Loading dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.
Subsequent doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.
Total duration of treatment: 1 year

B. Weekly regimen

Following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide chemotherapy, with either

· paclitaxel (weekly or 3-weekly schedule) for 12 weeks, then as a single agent for a further 40 weeks; or

· docetaxel or docetaxel and carboplatin (3-weekly schedule for 6 cycles (18 weeks), then as a single agent during treatment with chemotherapy.

Loading dose: an initial dose of 4 mg/kg body weight administered as a 90 minute intravenous infusion.
Subsequent doses: 1 week after the loading dose administer 2 mg/kg body weight at weekly

intervals. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Locally advanced breast cancer

With neoadjuvant doxorubicin and paclitaxel, until surgery and continued as a single agent following surgery, for a total of 1 year.

Loading dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Metastatic Breast Cancer

Loading Dose: The recommended initial loading dose is HERCEPTIN 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent Doses: The recommended weekly dose of HERCEPTIN is 2 mg/kg body weight given at weekly intervals. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

In clinical trials, patients with metastatic breast cancer were treated with HERCEPTIN until progression of disease.

Adverse effects: febrile neutropenia, anaemia, thrombocytopaenia, leukopenia, neutropenia; cardiac failure (congestive), reduced LVEF, cardiomyopathy, supraventricular tachyarrhythmias; erythema, rash, face swelling, palmar-plantar erythrodysaesthesia syndrome; diarrhoea, vomiting, nausea, abdominal pain; anorexia, weight loss; wheezing, dyspnea, cough, epistaxis, rhinorrhoea; conjunctivitis, increased lacrimation; tremor, dizziness, headache, peripheral neuropathy; arthralgia, myalgia, fatigue, pyrexia; asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion related reactions, pain, peripheral oedema.

Appendix 1: Interactions

Trastuzumab	
Anthracyclines	Increased risk of trastuzumab-induced cardiotoxic effects
Paclitaxel	Possible increased mean trough serum concentrations of trastuzumab and decreased trastuzumab clearance

Appendix 2: Pregnancy

Trastuzumab	Trastuzumab avoided during pregnancy and since it may persist in the circulation for up to 27 weeks, pregnancy should be avoided for 6 months after the last dose, unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

Appendix 3: Breastfeeding

Trastuzumab	Breast-feeding should be avoided during trastuzumab therapy and for 6 months after the last dose of trastuzumab.

Appendix 4: Renal impairment

Trastuzumab	Data suggest that the disposition of trastuzumab is not altered based on serum creatinine levels up to 177 µmol/l

Appendix 5: Hepatic impairment	
Trastuzumab	The use of trastuzumab in patients with hepatic impairment has not been studied.

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