Review of the available evidence on Trastuzumab for Inclusion in the WHO Essential Medicines List as an anti-neoplastic agent

Union for International Cancer Control
Route de Frontenex, 62
1207 Geneva
Switzerland

Dana-Farber Cancer Institute
Center for Global Cancer Medicine
450 Brookline Avenue
Boston, MA 02215

Persons to contact:

Lawrence N. Shulman, MD
Chief of Staff
Senior VP for Medical Affairs
Director, Center for Global Cancer Medicine
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: +1.617-632-2277
Fax: +1.617-632-2260
Email: lawrence_shulman@dfci.harvard.edu

Julie Torode, PhD
Deputy CEO, UICC
Route de Frontenex 62
1207, Geneva
Phone: +41.22 809 1811
Fax: +41.22 809 1810
Cell: +41.78 6939517
Email: torode@uicc.org
Table of Contents

1. Summary statement of the proposal for inclusion, change or deletion ......................... 4
2. Name of the focal point in WHO submitting or supporting the application ............... 4
3. Name of the organization(s) consulted and/or supporting the application .................. 5
4. International Non-proprietary Name (INN, generic name) of the medicine ................. 5
5. Formulation proposed for inclusion: including adult and paediatric (if appropriate) . . . . . . . . . . 5
6. International availability – sources, if possible manufacturers and trade names ............ 5
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group .............................................................................................................. 5
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population) ........................................ 6
   8.1 Introduction .............................................................................................................. 6
   8.2 Epidemiological information on disease burden and magnitude of treatment effect  7
   8.3 Early Stage Cancer ............................................................................................... 7
   8.4 Advanced or Metastatic Cancer ........................................................................... 8
   8.5 Assessment of current use .................................................................................... 8
   8.6 Target population ............................................................................................... 9
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills) ................................................................................................................................. 9
   9.1 Adjuvant therapy for early stage disease ............................................................. 9
   9.2 Metastatic ........................................................................................................... 10
   9.3 Dosage ................................................................................................................. 10
   9.4 Duration .............................................................................................................. 10
   9.5 Clinical Guidelines and Consensus Statements ..................................................... 10
   9.6 Need for Special Diagnostics ............................................................................. 12
   9.7 Treatment or Monitoring facilities and skills ....................................................... 15
10. Summary of comparative effectiveness in a variety of clinical settings .................... 15
    10.1 Summary of available estimates of comparative effectiveness .......................... 15
11. Summary of comparative evidence on safety ............................................................. 15
    11.1 Estimate of total patient exposure to date .......................................................... 16
    11.2 Description of adverse effects/reactions ........................................................... 16
    11.3 Identification of variation in safety due to health systems and patient factors ...... 16
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.................................................................17
13. Summary of regulatory status of the medicine (in country of origin, and preferable in other countries as well)...........................................................................................................18
15. Proposed (new/adapted) text for the WHO Model Formulary ........................................18
References: ..............................................................................................................................21
1. Summary statement of the proposal for inclusion, change or deletion

We are proposing the addition of trastuzumab to the WHO Essential Medicines anti-neoplastic list based on its role in substantially reducing mortality for women with early stage HER2 positive breast cancer, and the fact that there are no less costly medications that can be substituted and attain this effect.

Breast cancer remains one of the leading causes of cancer death in women world-wide, so there is an urgent need for more effective therapies. Approximately 20-25% of women with breast cancer will have tumors that over-express HER2, or have amplification of the HER2 gene. For women who have early stage breast cancer that over-express HER2 – with cancer confined to the breast and axillary lymph nodes – the addition of trastuzumab to chemotherapy reduces mortality by more than 30%. The data accumulated to date derives from eight clinical trials, four of which were very large and practice-changing. This is significant because patients with breast cancer and tumors over-expressing HER2 have a particularly dire prognosis when treated with chemotherapy alone, since these cancers are aggressive and have a high rate of metastatic spread.

The approval of trastuzumab added to chemotherapy as an adjuvant therapy for women with early stage HER2 positive breast cancer by the US FDA 7 years ago (in 2005) has led to the saving of thousands of lives per year in the US alone.

We feel that patients in all corners of the world should have access to this life saving agent, which is readily available and easily administered.

In addition, trastuzumab has been shown to significantly extend the life of patients with advanced HER2 positive breast cancer when added to standard chemotherapy. There are no less costly drugs which have this important benefit.

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

Dr Andreas Ullrich - Medical Officer
Chronic Diseases and Health Promotion
WHO focal point for Cancer Control
World Health Organization, HQ, Geneva

AND

Dr Cecilia Sepulveda - Senior Adviser
Chronic Diseases Prevention and Management
World Health Organization, HQ, Geneva
3. Name of the organization(s) consulted and/or supporting the application

The application has been developed by a working group from the Center for Global Cancer Medicine of the Dana Farber Cancer Institute, including Lawrence N. Shulman, M.D. and Lidia Schapira, M.D.

The covering letter details the process followed by the authors of the application.

4. International Non-proprietary Name (INN, generic name) of the medicine

Trastuzumab (INN was taken from WHO-Mednet INN list and EMA/FDA websites).

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

Trastuzumab 440 mg. Injection, powder + diluent for reconstitution, contains benzyl alcohol.

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

Herceptin vial 440 mg is manufactured by the following companies in the US:

- Genentech Inc., South San Francisco, CA, USA
- DSM Pharmaceuticals Inc., Greenville, NC, USA

Worldwide: manufactured and distributed by Roche Pharmaceuticals, Switzerland.

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

Trastuzumab is being proposed as an individual medicine.
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Introduction

One in four patients with early stage breast cancer have a HER2 positive tumor and these tend to be more aggressive with an increased recurrence rate, and in the case of patients with metastatic disease, shorter survival when compared to patients with HER2 negative, hormone receptor positive breast cancer.

Trastuzumab is a humanized monoclonal antibody with binding affinity for the HER2 receptor. It has an acceptable safety record and is not associated with the most common chemotherapy-related side effects. It has typically been paired with chemotherapy drugs known to be effective in treating the disease or with hormonal therapy. Thousands of women worldwide were enrolled in clinical trials which demonstrated significant reductions in cancer recurrence and mortality.

The data accumulated to date derives from eight clinical trials, four of which were very large and practice changing. Results of three randomized clinical trials published in 2005, reported that the combination of trastuzumab with chemotherapy drugs achieved a significant reduction in the rate of recurrence and improved survival. This led the US FDA to approve the drug as adjuvant therapy. A fourth clinical trial published in 2011 confirmed prior findings. It is important to note that the magnitude of the observed beneficial effect was consistent over all trials and showed an important improvement in survival.

Based on the majority of large randomized trials, the current accepted duration of therapy in the adjuvant setting is one year. The drug was administered intravenously either with chemotherapy or in a sequential fashion, i.e. after chemotherapy. Toxicities included minor infusion reactions and a small risk of reduction in cardiac function as assessed by a reduced left ventricular ejection fraction. Frank congestive heart failure was rare, and findings essentially always reverted to normal after cessation of trastuzumab. The benefits of using trastuzumab for women with HER2 positive disease far outweigh the risks and result in a significant reduction in risk of recurrence and of dying from this disease.

In the metastatic setting, trastuzumab is typically combined with chemotherapy, most frequently a taxane drug, and continued until the time of tumor progression. At the time of tumor progression, trastuzumab is continued and another chemotherapy agent is substituted for paclitaxel. New data suggests that the addition of pertuzumab to trastuzumab and a taxane further increases the duration of response.
8.2 Epidemiological information on disease burden and magnitude of treatment effect

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008. (Globocan latest available figures) Treatments that significantly impact on breast cancer related mortality need to be made available to women living in resource poor countries in order to reduce global health inequities. This means that one quarter to one fifth of breast cancer patients worldwide with HER2 over-expressing breast cancer should have access to this life saving therapy, including trastuzumab, which has been conclusively shown to decrease mortality. The magnitude of the treatment effect proved to be similar and consistent across different clinical trials: 50% decrease in rates of recurrence and 30% reduction in breast cancer related mortality. As far as cancer treatments are concerned, this benefit is universally accepted as extremely significant and practice changing.

8.3 Early Stage Cancer

Early breast cancer refers to tumors that are confined to the breast and adjacent groups of lymph nodes, typically in the axilla. With access to appropriate treatment, most patients with early stage breast cancer can hope to be cured of their disease. Treatment typically requires the removal of the primary tumor via surgical excision. Women who have limited surgery, i.e. lumpectomy or quadrantectomy also require treatment with radiation. In some cases the addition of radiation is also recommended even after removal of the entire breast via mastectomy. Systemic adjuvant therapies can substantially reduce the risk of breast cancer recurrence and death by eliminating sub-clinical micrometastases.

Adjuvant therapy is chosen based on the biological drivers of growth of the primary tumor. Hormone blocking treatment, also known as endocrine or antiestrogen therapy, is very effective for approximately two thirds of all patients whose tumors are estrogen receptor positive and hormonally sensitive. Chemotherapy is effective across all tumor types, although its principal use is for tumors that are hormonally insensitive and those that over-express HER2.

For patients with HER2 overexpressing breast cancer Level 1 evidence supports adding trastuzumab to standard chemotherapy. Four large clinical trials and four minor trials that collectively involved 11,991 women showed a reduction in risk of recurrence of 50% and reduction in the risk of death of 30%. All the trials establishing the benefit of trastuzumab limited eligibility to women with either node-positive disease or high risk node-negative disease. In the National Surgical and Breast and Bowel Project 31 trial (NSABP- B-31) women with HER2 positive and node-positive disease received either four cycles of single agent paclitaxel given every three weeks with or without trastuzumab
and then completed a year of trastuzumab. In the North Central Cancer Treatment Group (NCCTG) coordinated Intergroup trial N-9831, women with HER-2 positive node–positive or high risk node-negative disease were treated with weekly paclitaxel followed by no further treatment, weekly paclitaxel followed by sequential trastuzumab for 52 weeks and weekly palciataxel with concurrent trastuzumab for 12 weeks followed by trastuzumab alone for 52 weeks.\textsuperscript{22}

Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer in a joint analysis of data from NCCTG N9831 and NSABP B-31 showed that for patients receiving trastuzumab there was significantly increased DFS (HR = 0.52; 95% CI, 0.45-0.60), and OS as well (HR = 0.61; 95% CI 0.50-0.75).\textsuperscript{22} At 4 years 93% of patients receiving trastuzumab were alive as compared to 85.6% for those not receiving the drug. This represented a 39% reduction in the chance of death for those patients receiving trastuzumab.

\section*{8.4 Advanced or Metastatic Cancer}

Metastatic cancer refers to any cancer that has spread beyond the organ of origin. In the case of breast cancer, this refers to situations where cancer that started in breast is found in sites other than the draining lymph nodes, such as bones, liver, lungs, and brain. Biologically it remains breast cancer and ought to be treated as such. About 5% of women in developed countries have metastatic breast cancer when they are first diagnosed and the percentage is much higher in developing countries without access to screening or early detection. Women who were diagnosed with early stage HER 2 over-expressing breast cancer may experience a recurrence of disease after their initial treatment and this typically occurs in the first 3 years.

Patients diagnosed with metastatic HER2 over-expressing breast cancer may derive meaningful responses to treatment with improvement in quality of life, reduction of symptoms and prolongation of life by months or years. Access to effective treatment even when cure is no longer possible constitutes an important advance in treatment of this disease and is currently limited to women in countries with greater resources. Trastuzumab has been shown in multiple trials to significantly prolong survival for these patients.

\section*{8.5 Assessment of current use}

Trastuzumab is always paired with a standard chemotherapy drug as starting treatment but it can also be continued alone or with endocrine therapy, such as aromatase inhibitors or tamoxifen. Chemotherapy agents paired with trastuzumab include taxanes and vinorelbine.
8.6 Target population

The target population includes women with early stage, locally advanced or metastatic breast cancer that over-expresses HER2. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for trastuzumab therapy because these are the only patients studied for whom benefit has been shown. Tests should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

9.1 Adjuvant therapy for early stage disease

Review of eight trials included in the Cochrane Review included 11,991 women with HER2 early stage, operable breast cancer who were assigned randomly to receive standard chemotherapy with or without trastuzumab. The four large studies are known as HERA, N9831, B-31 and BCIRG006.\textsuperscript{7,22,23,31}

Mean age of participants was 49 years and those with advanced or metastatic disease were excluded. More than 7,000 women were assigned by chance alone to a trastuzumab-containing treatment and almost 5,000 to a treatment without trastuzumab. Most of the women enrolled had cancer found in their axillary nodes or were considered at high risk for relapse but did not have involvement of axillary nodes. Four trials included patients with both (axillary) node positive and node negative breast cancer. In order to enroll in the study, women with no cancer in axillary nodes had tumors that were larger than 2 cm (N9831, B31) or 1 cm (HERA).

The joint analysis of the B31 and N9831 trials demonstrated that the addition of one year of trastuzumab to sequential chemotherapy (with anthracyclines and taxanes) reduced the risk of recurrence by approximately half and the risk of death by one third.\textsuperscript{22} A similar benefit was seen in the HERA trial for patients randomly assigned to 1 year of trastuzumab given after completion of their usual chemotherapy.\textsuperscript{23} A fourth study (BCIRG006) employed a different design in order to ascertain if anthracyclines, one of the most frequently used chemotherapy agents with potential toxicity to the heart muscle, could be safely omitted without inferior results.\textsuperscript{31} Results were published towards the end of 2011 and showed there was indeed another option for treatment with comparable results and fewer cardiac sequelae.
9.2 Metastatic

In a landmark study published in 2001, Slamon was able to show that for patients with metastatic breast cancer that overexpressed HER2, those who received combinations of chemotherapy and trastuzumab survived longer than patients who received chemotherapy alone. This trial was the basis for the US FDA approval of trastuzumab in the metastatic setting. The results have since been confirmed and serve as the basis of combination therapies for women with Stage IV disease. More recently, several HER2 directed therapies have been combined with promising results.

9.3 Dosage

The dosage is the same for all indications and is based on the weight of the patient. There are two common schedules. The weekly dosing schedule provides an initial dose of 4 mg/kg as a 90-minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions. The every 3 week regimen employs a larger initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

Trastuzumab has been most extensively studied when given in conjunction with cytotoxic chemotherapy, most frequently with a taxane, or after anthracycline based regimens. This is based on pre-clinical data suggesting significant synergy between chemotherapy and trastuzumab.

9.4 Duration

In the adjuvant setting, one year is the generally accepted reference duration for trastuzumab therapy based on the pivotal trial protocols (HERA, N9831,B31, BCIRG006).

In the metastatic setting, trastuzumab and chemotherapy are generally continued until there is evidence of tumor progression. At that time chemotherapy agents are frequently changed, and trastuzumab continued.

9.5 Clinical Guidelines and Consensus Statements

The National Comprehensive Cancer Network (NCCN®) clinical practice guidelines in oncology recommend the following adjuvant chemotherapy regimens for HER2-positive breast cancer:

10
• Trastuzumab-preferred adjuvant regimens:

  o Doxorubicin, cyclophosphamide followed by paclitaxel + Trastuzumab, various schedules (AC followed by T + concurrent Trastuzumab)
  o Docetaxel, carboplatin, trastuzumab (THC)

• Other Trastuzumab adjuvant regimens:

  o Docetaxel + Trastuzumab followed by fluorouracil/epirubicin/cyclophosphamide (FEC)
  o Chemotherapy followed by, trastuzumab sequentially
  o AC followed by docetaxel + trastuzumab

The NCCN guidelines recommend the following as preferred chemotherapy regimens for HER2-positive recurrent or metastatic breast cancer:

• Preferred first-line agents:

  o Pertuzumab + trastuzumab + docetaxel
  o Pertuzumab + trastuzumab + paclitaxel

• Other First-line Agents for HER2-positive disease:

  o Trastuzumab with paclitaxel ± carboplatin
  o Trastuzumab with docetaxel
  o Trastuzumab with vinorelbine
  o Trastuzumab with capecitabine

• Agents for Trastuzumab -exposed HER2-positive disease:

  o Lapatinib + capecitabine
  o Trastuzumab + capecitabine
  o Trastuzumab + lapatinib (without cytotoxic therapy)
  o Trastuzumab + other agents

The NCCN guidelines provide further details on the recommended dosing and schedules for the various chemotherapy regimens. Additional details can be found at http://www.nccn.org.
The European Society for Medical Oncology (ESMO) clinical practice guidelines for primary breast cancer recommends trastuzumab and chemotherapy for the adjuvant/neoadjuvant treatment of HER2-positive breast cancer (parallel with taxane in adjuvant and added to primary chemotherapy in neoadjuvant).\textsuperscript{10}

The ESMO guidelines for metastatic breast cancer state that trastuzumab with or without chemotherapy should be offered early to all HER2-positive breast cancer patients.\textsuperscript{24} Trastuzumab or lapatinib in combination with endocrine therapy is listed as an option for patients with estrogen/progesterone receptor-positive and HER2-positive tumors who do not require or are unable to tolerate chemotherapy with anti-HER2 therapy. In addition, the guidelines include trastuzumab in combination with lapatinib for patients progressing on anthracyclines, taxanes, and trastuzumab.

In addition, a third consensus statement on medical treatment of metastatic breast cancer generated by the Central European Cooperative Oncology Group (CECOG) recommends trastuzumab for the treatment of metastatic breast cancer in patients with HER2 overexpression.\textsuperscript{35} The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) recommend trastuzumab for the treatment of early and metastatic breast cancer in select older patients.\textsuperscript{2}

### 9.6 Need for Special Diagnostics

Overexpression or amplification of HER2 has been observed in approximately 25% of breast cancer patients, and is correlated with poor clinical outcomes in patients not treated with HER2-directed therapy.\textsuperscript{5,8} Consequently, the use of reliable and accurate testing methods to identify patients with HER2-positive breast cancer is key to providing prognostic information and selecting the patients most likely to benefit from trastuzumab therapy.

#### HER2 Assays

There are a number of different tests that assess various aspects of HER2 status:

- FISH, CISH, SISH, or polymerase chain reaction (PCR) assays assess HER2 gene amplification through a count of HER2 gene copies.
- IHC provides a semiquantitative assessment of HER2 protein expression on the tumor cell surface.
• An enzyme-linked immunosorbent assay (ELISA) measures the level of circulating HER2 receptor protein.

In the United States, IHC, FISH, Dual ISH, and CISH assays have been approved for selecting appropriate patients for Herceptin therapy. Guidelines from ASCO/CAP and the National Comprehensive Cancer Network (NCCN) recognize HER2 status assessment with IHC and/or FISH. Currently, there is no gold standard for evaluating the accuracy of a test; no assay can identify with perfect accuracy all patients who are potentially expected to benefit from Trastuzumab therapy.

The Herceptin pivotal clinical trials for MBC utilized Clinical Trial Assay (CTA) IHC testing by a central reference laboratory to determine appropriate patients for enrollment. Patients were eligible for study treatment if they were IHC 2+ or 3+. The HercepTest® was developed to provide an alternative to the investigational CTA used in the pivotal trial. The performance of HercepTest was evaluated independently by comparing results of HercepTest to CTA on breast tumor specimens (not from Herceptin clinical trials). Data and retrospective analysis from the pivotal trials suggest that beneficial treatment effects were largely limited to patients whose tumors tested IHC 3+ by CTA and HercepTest (defined as strong membrane staining of >10% of tumor cells, with no staining of normal epithelial cells within the same section and/or FISH(+) by PathVysion®).

The assay type used in the pivotal MBC clinical trials was subsequently standardized, and concordance was established with certain commercially available assays. As with other laboratory tests and procedures, the accuracy or reliability of the determination of protein overexpression or gene amplification is affected by factors such as the sensitivity and specificity of the particular assay; use of commercial or compounded reagents; employment of and adherence to standardized or validated assay procedures; and the expertise of the laboratory.

Concordance rates between FISH and IHC assays have reportedly ranged from 73% to 95%, with higher levels of concordance in tumor blocks measuring as FISH(+) and IHC 3+. In contrast, Garcia-Caballero et al. reported that only 18% of specimens that were DAKO HercepTest 2+ were found to be FISH(+). High concordance rates between FISH and CISH (94.9%) and between CISH and IHC (92.6%) have also been reported.

In the Herceptin pivotal clinical trials in the adjuvant breast cancer setting, patient samples were tested by IHC and FISH. Patients were eligible for study if they were IHC 3+, defined as >10% of invasive tumor cells with uniform intense staining and/or FISH(+), defined as a HER:CEP17 ratio of >2. The BCIRG 006 study required as a patient eligibility criterion HER2 gene amplification. Tumor blocks were sent to designated central laboratories for HER2 testing by FISH (Vysis Kit).
HER2 Testing Guidelines

Both the ASCO/CAP guideline for HER2 testing in breast cancer and the NCCN breast cancer guideline categorize HER2 testing results into 3 categories: positive, equivocal, or negative for HER2. Each category may lead to a different clinical decision for patients with invasive breast cancer.\(^4,18,28,40\) In the ASCO/CAP guideline, samples are categorized as IHC 3+ if they demonstrate uniform intense staining in >30% of invasive tumor cells, and as FISH(+) if they demonstrate a HER2/CEP17 ratio >2.2. In the Herceptin adjuvant trials, patients were considered eligible for study if their samples were IHC 3+, defined as >10% of tumor cells with intense staining, or FISH(+), defined as HER2/CEP17 ratio ≥2. The following figure summarizes the testing guidelines for the FISH and IHC assays.

\[\text{HER2 Testing [9-12]}\]

**IHC Testing**

- IHC 3+
  - HER2 Positive
- IHC 2+
  - Equivocal (Borderline)
  - Test with FISH
- IHC 0 or IHC 1+
  - HER2 Negative

**FISH Testing**

- FISH ratio\(^{*}\) >2.2 or HER2 gene copy\(^{†}\) >6.0
  - HER2 Positive
  - Count additional cells
  - FISH retest
  - Test with IHC
- FISH ratio 1.8-2.2\(^{‡}\) or HER2 gene copy 4.0-8.0
  - Equivocal (Borderline)
- FISH ratio <1.8 or HER2 gene copy <4.0
  - HER2 Negative

Notes: \(^{*}\)IHC 3+ is defined by the ASCO/CAP Guidelines as >30% of invasive tumor cells with uniform intense staining. In the pivotal adjuvant Herceptin trials, IHC 3+ was defined as >10% of invasive tumor cells with uniform intense staining.

\(^{†}\)FISH ratio=HER2/CEP 17 ratio, where CEP 17 is a centromeric probe for chromosome 17 on which the HER2 gene resides.

\(^{‡}\)Equivocal HER2 gene amplification where patients with HER2/CEP17 ratio ≥2.0 were eligible for the Herceptin adjuvant trials.

Abbreviations: FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor type 2; IHC=immunohistochemistry.
9.7 Treatment or Monitoring facilities and skills

- Facilities with capacity to administer intravenous infusions
- Facilities with capacity to administer intravenous cytotoxic and biologic therapies
- Ability to do HER2 testing on tumor tissue
- Ability to assess left ventricular ejection fraction

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

We identified a systematic review performed by the Cochrane group and published in 2012. This review collected data from RCT’s comparing the efficacy and safety of trastuzumab alone or in combination with chemotherapy or no treatment, or standard chemotherapy alone, in women with HER2 positive early breast cancer including women with locally advanced breast cancer. They included eight studies involving 11,991 patients. The combined hazard rates for overall survival and disease-free survival significantly favored the trastuzumab containing regimens. Trastuzumab significantly increased the risk of congestive heart failure and asymptomatic left ventricular ejection fraction decline which did not lead to loss of life. The authors concluded that trastuzumab improves survival for women with HER2 overexpressing breast cancer.13

10.1 Summary of available estimates of comparative effectiveness

There are no similar agents which accomplish the same improvement in patient survival.

Cost estimates need to consider the cost of lives lost due to no therapy, suffering and interruption of productive lives for young women experiencing early death or relapse.

11. Summary of comparative evidence on safety

There is no comparable drug in adjuvant or metastatic setting that is less expensive. Several new, and more expensive, less tested drugs are under development or recently approved by the FDA (pertuzumab, T-DM-1).
11.1 Estimate of total patient exposure to date

Since it was first marketed in September 1998, until October 2008, more than 420,000 women with breast cancer had been treated with trastuzumab worldwide.

11.2 Description of adverse effects/reactions

Adverse effects and reactions of trastuzumab include cardiovascular (palpitations, tachycardia, peripheral edema, cardiomyopathy, congestive heart failure (CHF), declines in left ventricular ejection fraction (LVEF), CNS effects (pain, fever, chills, headache, insomnia), dermatologic (rash, irritation), gastrointestinal (nausea, vomiting, intestinal pain, diarrhea, anorexia), neuromuscular and skeletal (weakness, back pain, bone pain, dizziness), respiratory (cough, dyspnea, rhinitis, pharyngitis, flu-like symptoms), infusion reactions (hypersensitivity, chills, fever), infection, anemia, allergic or anaphylactoid reactions.

Data on CHF is available from 8 clinical trials, totaling 10,281 patients with early breast cancer. There 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.

Data on LVEF is available from 7 clinical trials, totaling 7939 patients. There were 466 (11.2%) of LVEF decline out of 4147 patients in the trastuzumab group, and 215 (5.6%) cases out of 3792 patients in the control group. Almost all patients had reversal of LVEF suppression after discontinuation of trastuzumab.

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

The incidence of cardiac toxicities seems to be higher in regimens where trastuzumab was given for a longer period: the risk of severe CHF when trastuzumab was used for more than 6 months is estimated to be more than ten times higher than in those where trastuzumab was administered for less time. The data reached statistical significance on comparison, and heterogeneity across clinical trials was minimal.

In patients receiving trastuzumab sequentially after standard chemotherapy, the risks of LVEF decline seemed higher than in those patients receiving it concurrently with chemotherapy. However the data here must be interpreted with caution, since the higher risk in the sequential subgroup might be explained by different cardiotoxicity of the chemotherapy preceding trastuzumab. This potential difference needs to be further explored in clinical trials.
It must be taken into account that the safety data presented here is extracted from analyses of clinical trials in which women were generally younger, healthier, and all had measured LVEF of 55% or higher. These conditions may not necessarily reflect general clinical practice.

Careful attention is needed in patient selection, particularly in women with a low risk of recurrence, such as patients with small tumors, and negative lymph nodes. This is important so that the substantial gains in mortality reduction achievable with trastuzumab are not eroded by cardiac toxicity.

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

Since the discovery of trastuzumab in the late 1980’s and the landmark studies that led to its approval in the US and Europe in the 1990’s, other drugs have been developed and brought into the clinic. In the US, there are now three FDA approved anti HER2 drugs: trastuzumab, lapatinib and pertuzumab. Studies have compared efficacy and safety of the addition of lapatinib versus trastuzumab or their combination to neoadjuvant chemotherapy in HER-2 positive breast cancer.

A recent meta-analysis of randomized trials identified six trials with 1,494 eligible patients. The probability to achieve a pathologic CR was higher for trastuzumab plus chemotherapy versus lapatinib plus chemotherapy. Probability to pathologic CR was higher in the group receiving combination anti HER2 therapy. Grade III-IV toxicities consisted of diarrhea and dermatologic problems and were seen more frequently in patients receiving lapatinib. No differences were observed in terms of cardiac toxicity. This data supports the superiority of dual anti-HER2 inhibition in the preoperative setting and support the superiority of trastuzumab over lapatinib. Research efforts are now directed at overcoming resistance to trastuzumab by designing new molecules with complementary or synergistic mechanisms of action. An example of this class of drugs is pertuzumab, a new anti-HER2 humanized monoclonal antibody that prevents the formation of HER2 dimers. It has been used as a single agent and combined with trastuzumab with promising results. The most recent international study, CLEOPATRA, reported favorable outcomes thus establishing a new milestone for the treatment of this disease. As more refined strategies emerge and more treatments become available, the gap between those with and without access to HER2 directed therapy will widen with worse outcomes in resource poor countries.

Cost effectiveness analyses have been conducted in many countries over the past decade with various results. Comparison of trastuzumab versus chemotherapy without trastuzumab shows promise but long-term effects are still uncertain and further research will be required to answer these questions conclusively.
13. Summary of regulatory status of the medicine (in country of origin, and preferable in other countries as well)

Trastuzumab is currently approved in over 120 countries. The first marketing authorization for trastuzumab was granted in the United States of America. It is also approved in the European Union and Switzerland. HER2 testing is mandatory prior to initiation of trastuzumab therapy. Trastuzumab should be administered by a qualified health care professional.

The approved indications and instructions for use may differ from one country to another. The label approved by Regulatory Agency in the country or in the country of reference should be followed.


US Pharmacopoeia
British Pharmacopoeia
European Pharmacopoeia
International Pharmacopoeia

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

Trastuzumab 440mg
Injection, powder, with accompanying diluent (contains benzyl alcohol)

Uses:

Adjuvant: Treatment of HER2-overexpressing breast cancer, as part of a combination regimen with doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; in combination with docetaxel and carboplatin.

Adjuvant single agent Following anthracycline-based combination treatment. First line metastatic disease: Treatment of HER2-overexpressing breast cancer in combination with paclitaxel. Single agent therapy in patients with metastatic disease; who have received prior chemotherapy for treatment of HER2-overexpressing metastatic disease
Precautions:

**Cardiac toxicity** - symptomatic and asymptomatic declines in LVEF, and heart failure. Evaluate LVEF prior to and during treatment. Use caution in patients with pre-existing cardiac disease, or in patients who have received prior chest irradiation. Other risk factors include diabetes, advanced age, low body mass index, hyper- or hypo-thyroidism. Cardiac toxicity may be reversible within 1-3 months.

**Infusion reactions** - Serious reactions have occurred. Consider pre-medication with corticosteroids, H-1 and H-2 blockers to prevent. Infusion reactions may occur despite premedication. Monitor patient closely during infusions, and stop infusion for dyspnea, chest pain, hypotension, or signs of weakness.

**Pulmonary** – Trastuzumab may cause serious pulmonary toxicity (dyspnea, hypoxia, pulmonary infiltrates, pulmonary fibrosis). Use cautiously in patients with pre-existing pulmonary disease or extensive pulmonary involvement. These reactions may occur 24 hours or later after infusion.

**Pregnancy** - Trastuzumab may cause fetal harm or fetal death. Effective contraception is recommended during and for 6 months following treatment in women of childbearing potential.

**Special handling** – Trastuzumab is a biologic agent, and should be handled and disposed of using biohazard precautions.

Dosage:

**Weekly dosing scheme:**  
4mg/kg over 90 minutes  
Subsequent doses: 1 week delay, then  
2mg/kg over 30 minutes  
Repeat 2mg/kg weekly  
until therapy completed

**Every three week dosing scheme:**  
8mg/kg over 90 minutes  
Subsequent doses: 3 week delay, then  
6mg/kg over 30-90 minutes  
Repeat 6mg/kg every 3 weeks  
until therapy completed

**Adverse effects**

**Cardiovascular:** LVEF declines, peripheral edema, heart failure, tachycardia, hypertension, arrhythmia, palpitations (see boxed warning in Precautions)
Central Nervous System: pain, fever, chills, headache, dizziness

Dermatologic: rash, irritation

Gastrointestinal: nausea, diarrhea, vomiting, abdominal pain, anorexia

Neuromuscular/Skeletal: weakness, pain, paresthesia, bone pain, arthralgias, myalgia

Respiratory: cough, dyspnea, rhinitis, pharyngitis, URI infection

Hematologic: anemia, leukopenia

Infusion Reactions: (see boxed warning in Precautions)

Drug Storage

Trastuzumab (Herceptin®) must be stored in a refrigerator between 2-8°C before use.

Drug Preparation

Trastuzumab is supplied in a combination package that contains the active drug as a dry powder, with a diluent vial to be used to reconstitute the drug. The diluent vial contains benzyl alcohol preservative. Once reconstituted, the resulting solution contains trastuzumab 21mg/mL. The reconstituted solution is stable under refrigeration 2-8° for 28 days. Do not freeze.
References:


