Expert peer review on application for trastuzumab

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes ✓ No (if no, please provide reference and information)

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Adjuvant therapy. 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% in relative terms: for survival for example at 4 years 93% of patients receiving trastuzumab were alive as compared to 85.6% for those not receiving the drug.

   Advanced breast cancer. 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 (20% more) than patients who received chemotherapy alone (median survival, 25.1 vs. 20.3 months; rate of death at 1 year (22 percent vs. 33 percent, P=0.008.)

   c. Please provide any additional relevant information with reference

   A recent Cochrane reviews (Moja et al, 2012, quoted in the application) shows that a beneficial effect for both OS and DFS is seen in women with HER2-positive breast cancer with a moderate-to-high risk of recurrences. This indicated the need to carefully select the women candidate for treatment.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✓ No (if no, please provide reference and information)

   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   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.

   Almost all patients had reversal of CHF after discontinuation of trastuzumab. 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.
c. Please provide any additional relevant information with reference

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.

3. Assessment of cost and availability
a. Have all relevant data on safety provided
   Yes ☑ No (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Not much information is available on actual cost in various countries as a basis to inform affordability issues. Data on cost effectiveness are favourable for high income countries.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

Generic manufacturers are now available in various countries.

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

It is a treatment option for a 20-25% women positive for HER2. In adjuvant settings for medium and high risk women it can offer a relevant clinical benefit. In metastatic setting it can be defined as a moderately effective treatment option until relapse.

Suggested duration of trastuzumab therapy is probably 6 months since longer duration (12 months) have a higher incidence of heart failure due to drug induced cardiac toxicity. Shorter duration (3 months) have also been tested. The benefits are minimal for small tumours and in node-negative patients.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

ASCO and NCCN and other international guidelines strongly recommend trastuzumab as standard treatment.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

An overall capacity of health system should be available when considering trastuzumab in terms of screening, surgery and radiotherapy. Full capacity to monitor intravenous chemotherapy is needed.

It also requires specific diagnostic capacity to define HER2 status with both
- IHC provides a semiquantitative assessment of HER2 protein expression on the tumor cell surface (as a first screening test).
- FISH, CISH, SISH, or polymerase chain reaction (PCR) assays assess HER2 gene amplification through a count of HER2 gene copies (for equivocal IHC 2+).
Finally it requires a capacity to monitor left ventricular function by echocardiography over time.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes ✓ No

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

   In settings where health system have a good capacity to deliver mammographic screening, have surgical and radiotherapy capacity, have access to testing methods to identify patients with HER2-positive breast cancer and have a good monitoring capacity to administer conventional chemotherapy, trastuzumab can be recommended as an essential medicine.