19th Expert Committee on The Selection and Use of Essential Medicines
April 8-12 2013

Expert peer review on application for TRASTAZUMAB

INTRODUCTION

Two applications have been submitted for the inclusion of trastuzumab on the EML. The indication proposed is treatment of HER2 positive breast cancer, estimated to be 20-25% of all breast cancer cases.

The applications provide a comprehensive review of the literature.

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

   In early HER2 positive breast cancer, the use of trastuzumab in combination with standard treatment (surgery, radiotherapy and chemotherapy) has been found to increase the likelihood of survival, based on a meta-analysis of 8 trials. The estimated relative effect from the review by Moja et al is presented as hazard ratios for overall survival (OS) and disease-free survival (DFS), of 0.66 (95% CI 0.57, 0.77) and 0.60 (95% CI 0.50, 0.71) respectively. The review notes that there is some risk of bias in the trials due to inadequate allocation concealment, and also notes that some of the trials were stopped early for benefit. The sensitivity analyses conducted in the review to examine these factors did not find changes in the relative effect size. The review also notes that there are two trials that have not been published, including approximately 2800 patients.

   In metastatic breast cancer the addition of trastuzumab to standard chemotherapy may be associated with prolonged survival but the magnitude of the effect is less clear. There is no summary estimate in the application as there is no current review, but the trial published in 2001 (Slamon et al) found an increase in 5 months in overall survival. However, other estimates have been less.

   c. Please provide any additional relevant information with reference

      NA

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)
The short term, haematological toxicity of trastazumab is well characterised, and can be managed with adequate supportive care. The major concern, however, is the cardiotoxicity, which is well quantified in Moja et al. The uncertainty about optimal regimen duration – 6 months or shorter versus 12 months - is therefore a critical question for research. Most centres currently use 12 months treatment.

c. Please provide any additional relevant information with reference

NA

3. Assessment of cost and availability
a. Have all relevant data on cost 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.

Currently trastazumab is very expensive although the application provides useful information about price variation across different health care settings. For high-income countries, treatment of early breast cancer with trastazumab has generally been accepted as cost-effective, although the cardiotoxicity may mean that the early estimates of cost-effectiveness need to be re-assessed. Treatment of metastatic breast cancer with trastazumab has not been consistently accepted as cost-effective.

The application makes the case that the addition of trastazumab to the WHO EML may provide leverage for price reduction, as was seen following the inclusion of antiretrovirals on the EML in 2002. Trastazumab would be the first monoclonal antibody to be listed.

c. Please provide any additional relevant information with reference

NA

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

There is limited availability in some of the middle income and transitional countries, such as Brazil.

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

The application describes the epidemiology of breast cancer and the increasing need for effective treatments.

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

Several international guidelines recommend use of trastazumab. There are no WHO guidelines identified.

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

YES.
Trastuzumab should only be provided in settings that are capable of managing chemotherapy and in the context of a cancer service that can provide surgery and radiotherapy as well as palliative care. The service also must provide access to appropriate and high quality diagnostic tests for hormone receptors, HER 2 status and cardiac function monitoring.

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

7. Any other comments

While the relative effect of trastuzumab is significant, the absolute survival gain is less clear. The review by Moja et al provides estimates of likely survival at 3 years based on applying the observed hazard ratio from the trials to populations with low, medium and high risk of recurrence. As is noted in the discussion section of the review, applying the observed estimates of effect for both benefits and harms to a low risk group indicates that the tradeoff in terms of survival without recurrence vs cardiotoxicity is quite difficult –

‘If 1000 women at low risk were not treated with trastuzumab, five of them would be expected to experience severe cardiac toxicity and 900 would be expected to survive at three years, whereas if they were treated with trastuzumab the numbers would be 26 and 933, respectively.’

This narrow margin of benefit emphasises the need for appropriate patient selection as well the importance of a health system that has the diagnostic, treatment and monitoring modalities required to manage use of trastuzumab.

The treatment regimens for HER 2 positive and negative breast cancer are in the table below. The EML currently lists nearly all of the medicines, except epirubicin, vinorelbine and capecitabine, for which there are alternative chemotherapy regimens. However the List does not include any options for endocrine treatment regimens other than tamoxifen and there may need to be consideration of the aromatase inhibitors, which are used in women who have hormone receptor positive/HER2 negative cancers. This type of cancer may be as frequent as HER 2 positive breast cancer. The chemotherapy of ‘triple negative’ breast cancer is adequately covered by the medicines on the EML.

**Recommended treatment regimens based on NCCN guidelines and UptoDate.**

<table>
<thead>
<tr>
<th>HER2 positive treatment regimens, early breast cancer</th>
<th>Doxorubicin, cyclophosphamide (AC) then paclitaxel + trastuzumab, Docetaxel, carboplatin, trastuzumab (THC) OR Docetaxel + Trastuzumab followed by fluorouracil/epirubicin/cyclophosphamide (FEC) AC followed by docetaxel + trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive recurrent or metastatic breast cancer:</td>
<td>Trastuzumab with paclitaxel ± carboplatin Trastuzumab with docetaxel Trastuzumab with vinorelbine Trastuzumab with capecitabine</td>
</tr>
<tr>
<td>HER 2 negative</td>
<td>Docetaxel plus cyclophosphamide (+/- then paclitaxel) Doxorubicin plus cyclophosphamide (+/- then paclitaxel) Cyclophosphamide (oral/IV) plus methotrexate and fluorouracil Fluorouracil, epirubicin, cyclophosphamide (+/- paclitaxel, docetaxel)</td>
</tr>
</tbody>
</table>
8. What is your recommendation to the committee (please provide the rationale)

Trastuzumab is only essential in the context of a health system that has already established the full range of cancer care facilities. I recommend that Section 8 of the EML be restructured to indicate a hierarchy of treatments for breast cancer, as has been done for the EML for children. In that context the addition of trastuzumab as a Step 2 essential medicine is appropriate, particularly given the potential political and advocacy value of including a monoclonal antibody on the EML. A draft structure for the EML for breast cancer is shown below.

<table>
<thead>
<tr>
<th>Breast cancer (assuming surgery and radiotherapy and palliative care are available).</th>
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</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td>cyclophosphamide (with mesna)</td>
</tr>
<tr>
<td>fluorouracil</td>
</tr>
<tr>
<td>methotrexate</td>
</tr>
<tr>
<td>anthracyclines - doxorubicin [epirubicin]</td>
</tr>
<tr>
<td>platinum compounds - carboplatin</td>
</tr>
<tr>
<td>taxanes – docetaxel. paclitaxel</td>
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<tr>
<td><strong>Step 2 (requires capacity for hormone receptor diagnostic tests)</strong></td>
</tr>
<tr>
<td>trastuzumab</td>
</tr>
<tr>
<td>tamoxifen</td>
</tr>
<tr>
<td>an aromatase inhibitor</td>
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</table>