Proposed medicines(s) for treatment of Early Stage Breast Cancer (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclophosphamide (oral &amp; IV)</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>doxorubicin</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>paclitaxel</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>docetaxel</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>methotrexate</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>fluorouracil</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>trastuzumab (HER2 positive)</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>□ anastrozole (HR positive)</td>
<td></td>
<td>✗</td>
</tr>
</tbody>
</table>

(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

Yes ✗ No □

According to the International Agency for Research on Cancer (IARC) breast cancer comprises one-quarter of all new cancer cases worldwide, with an estimated 1.67 million cases in 2012 alone. Although highly treatable with systemic therapy, surgery, and radiation therapy, breast cancer was the cause of death of approximately half a million women worldwide in 2012. The ratio of incidence to mortality in high-income, middle-income, and low-income countries varies drastically: the 5-year survival rate for breast cancer ranged from 12% survival in The Gambia, an extremely poor country, to 79% in South Korea, a high-income country. Women suffering from breast cancer in the developing world are more likely to present at later stages. Even in less developed regions of the world overall survival at 5 years for women treated for localized disease was 73.6% on average, compared to 47.4% with regional disease.

(2) Have all important studies that you are aware of been included in the application?

Yes ✗ No □
Useful information about worldwide incidence and 5-year survival by country and period is provided in the CONCORD-2 study report, Allemani C. Et al, Lancet 2014: http://dx.doi.org/10.1016/S0140-6736(14)62038-9.

For the assessment of the present application this reviewer has also referred to

- St. Gallen Consensus discussion, Breast Care 2013;8:102–109; DOI: 10.1159/000351193
- Linee Guida Neoplasie della mammella, AIOM (Italian Oncology Medicine Association), 2014; http://www.aiom.it/area+pubblica/area+medica/prodotti+scientifici/linee+guida/1%2C33%2C1%2C

(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes ☒ No ☐

HR Positive/HER2 Negative tumors

The recommendations offered in this section are generally endorsed. Hormone therapy reduces the risk of systemic recurrence by 50% though the absolute benefit relates to the overall risk of relapse which in turn relates to tumor size, grade, and axillary nodal involvement. However, since those patients who develop metastatic breast cancer almost always die of their disease, reducing the odds of systemic relapse greatly improves survival.

The recommendation “For postmenopausal patients use of aromatase inhibitors in place of tamoxifen, or after a course of tamoxifen had a small incremental benefit for reducing distant recurrences...” is supported by the meta-analysis of Dowsett M, et al. J Clin Oncol 28:509-518. 2010 which is also referred to elsewhere in the application.

This reviewer wonders whether the proposal of adding the entire third generation of aromatase inhibitors is appropriate. While waiting for the result of ongoing RCTs addressing possible differences in efficacy and/or safety among them, the most used in RCTs and/or the less expensive aromatase inhibitor should be selected. Therefore, the first suggested option is to only select anastrozole. One possible alternative strategy is to include letrozole along with anastrozole, since they are very similar active agents with similar efficacy and safety profile as documented in large scale RCTs (Breast International Group (BIG) 1-98 Collaborative Group. N Engl J Med 2005, 353: 2747-2757; And Duffy S, et al. Hum Reprod 2006; 21: 545-553).
The improvement in relapse-free survival with chemotherapy varied by biologic sub-type as well as overall risk of relapse, again based on tumor size, grade and axillary nodal status. This reviewer concurs with the last two statements of this section regarding the use of chemotherapy in large cancers and involvement of axillary lymph nodes, and as neo-adjuvant treatment in operable patients.

Some data seem to challenge those statements. The meta-analysis by Mauri et al. (J Natl Cancer Inst 2005;97:188–94) evaluated nine randomized studies, including a total of 3946 patients with breast cancer and compared neoadjuvant therapy with adjuvant therapy regardless of what additional surgery and/or radiation treatment was used. Neoadjuvant therapy was apparently equivalent to adjuvant therapy in terms of survival and overall disease progression, but was associated with a statistically significant increased risk of loco-regional recurrence when radiotherapy without surgery was adopted. However, it is recognized that the neo-adjuvant chemotherapy is meant to allow a more conservative subsequent surgery which has an impact on the quality of life. Moreover, a small subset of patients may experience a pCR that predicts a longer survival. Since this only applies to a subset of patients, neo-adjuvant chemotherapy is not expected to affect survival in the overall population.

HR Positive/HER2 Positive tumors
On the basis of the Cochrane SR by Moja et al (2012) it is agreed that trastuzumab should be administered with chemotherapy and a taxane, but not concurrently with an anthracycline. As discussed below in the section dealing with HR/HER2 negative patients, this reviewer believes that paclitaxel should be preferred to docetaxel and included in the EML as the only taxane.

The wording regarding the possible benefit of pertuzumab as an add-on to neo-adjuvant trastuzumab and a taxane should be more cautious as evidence is based on preliminary findings of pathological response from a sponsor-driven phase 2 trial.

<table>
<thead>
<tr>
<th>2) HR Positive/HER2 Positive tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>As above, hormone therapy should always be a component of the therapy for these patients.</td>
</tr>
<tr>
<td>Chemotherapy plus trastuzumab should be administered to all patients but those with very small, node negative tumors (&lt; 0.5 cm). Typically trastuzumab is given concurrently with a taxane, and not administered concurrently with an anthracycline. Trastuzumab should be administered for a year. For patients receiving pre-operative therapy the combination of a taxane, trastuzumab and pertuzumab has been shown to be more effective than a taxane and trastuzumab alone. The addition of pertuzumab as part of post-operative adjuvant therapy has not been shown to be beneficial. The role of T-DM1 as adjuvant therapy remains undefined.</td>
</tr>
</tbody>
</table>

Since the addition of pertuzumab as part of post-operative adjuvant therapy has not been shown to be beneficial, it is agreed that pertuzumab inclusion in the EML is not proposed.

**HR Negative/HER2 Positive tumors**
It is agreed that hormone therapy is not indicated, while trastuzumab-chemotherapy combinations are indicated as reported in the previous section.

**HR Negative/HER2 Negative tumors**
Hormone therapies and trastuzumab containing regimens are not indicated for these patients. Chemotherapy regimens suggested (see table below) are agreed with the possible exception of docetaxel as an alternative to paclitaxel. The latter should be preferred because of its lower cost and should be the sole taxane allowed onto the EML.
This reviewer also wonders whether there is sufficient evidence to support the inclusion of epirubicin along with doxorubicin in the EML.

A systematic review and meta-analysis aimed at clarifying the risk of early and late cardiotoxicity of anthracycline agents (Smith et al. BMC Cancer 2010, 10:337) concluded that “evidence is not sufficiently robust to support clear evidence-based recommendations on different anthracycline treatment regimens, or for routine use of cardiac protective agents or liposomal formulations”.

A clinical review by Khasraw M. et al (Breast 2012; 21:142-9) concluded that “the cumulative epirubicin cardiac toxicity across all trials are less than 1%-2.5% which is similar to the rates observed in studies using doxorubicin”, being the efficacy of the two drugs equivalent.
(4) Does the application provide adequate evidence of safety for the proposed treatment regimen(s)? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☒  No ☐

The Applicant has carefully addressed the issue, in particular the cardiotoxicity of anthracyclines and trastuzumab whose risk is increased by the administration of both agents together, which should be avoided.

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?

Yes ☒  No ☐

Incisional biopsy rather than ultrasound-guided needle technique is useful to distinguish between in-situ and invasive cancer and to provide experienced pathologists with material for the histological diagnosis (ductal, lobular, etc.) and the immunohistochemistry analyses revealing estrogen, progesterone and HER2 receptors. CT scan and bone scan are also needed in order to rule out the presence of metastases. Hypersensitivity medications to face allergic reactions to taxanes and anti-emetics are required. There also is a need for monitoring blood cell count, renal function, electrolytes and liver functions. Out-patients infusion facilities are needed to administer chemotherapy and trastuzumab. Cardiac monitoring is recommended for patients receiving an anthracycline and/or trastuzumab. In the light of these considerations this reviewer does not support the following statement reported in the application.

Administration and Care of Patients:

Hormone therapies are largely oral (tamoxifen and aromatase inhibitors). No special testing or administrative resources are necessary for the utilization of these drugs, though a reliable supply is important.

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐  No ☒

This reviewer is not aware of any particular regulatory issue regarding trastuzumab or anastrozole.
European and Australian agencies recommend the use of aromatase inhibitors as an alternative to tamoxifen. The American Society of Clinical Oncology recommends their use initially for adjuvant therapy in early breast cancer. It suggests that an aromatase inhibitor should be included at the beginning as treatment of choice or after 2-3 years with tamoxifen.
Comment briefly on issues regarding cost and affordability of treatment.

The cost of both trastuzumab and anastrozole may be hardly affordable in several settings.

Any additional comments on the application?

Tamoxifen requires conversion into active metabolites (Z)-4-hydroxytamoxifen and (Z)-endoxifen that have up to 100-fold higher ER affinity than the parent drug. The cytochrome P450 enzyme CYP2D6 has a major role in the formation of endoxifen in postmenopausal women. A recent study (Saladores P. et al. The Pharmacogenomics Journal 2015; 15:84–94) addressed genetic variants of drug metabolizing enzymes as possible biomarkers for the prediction of clinical outcome and showed that tamoxifen efficacy in premenopausal breast cancer patients is influenced by CYP2D6-mediated metabolism. Therapeutic drug level monitoring at steady-state could identify patients with high endoxifen levels expected to have a lower risk of recurrence and who should therefore be encouraged to adhere to tamoxifen.

Please summarise the action(s) you propose the Expert Committee take.

The recommendations reported in the present application are generally endorsed. The proposal of adding trastuzumab and anastrozole in the EML is agreed.

This reviewer is skeptical about the proposal to include
- All the third generation of aromatase inhibitor, including letrozole and exemestane along with anastrozole
- Docetaxel along with paclitaxel
- Epirubicin along with doxorubicine.

This reviewer is of the opinion that for early breast cancer only trastzumab, anastrozole, paclitaxel and doxorubicin should be in the list. Other aromatase inhibitors, docetaxel, and epirubicin should not.

The medicines that are considered suitable to the EML on the basis of their (cost-)effectiveness should also be seen in the light of their affordability and of how far the WHO considers affordable costs as a requisite for the selection of essential medicines.