Proposed medicines(s) for treatment of Metastatic 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>doxorubicin</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>paclitaxel</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>trastuzumab (HER2 positive)</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>docetaxel</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>capecitabine</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>vinorelbine</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>gemcitabine</td>
<td>✗</td>
<td></td>
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<tr>
<td>cyclophosphamide</td>
<td>✗</td>
<td></td>
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<tr>
<td>tamoxifen</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>□ anastrozole (HR positive)</td>
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<td>✗</td>
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</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 □
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%2C333%2C1%2C

Other specific references are reported in the text.

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

Yes ☒ No ☐

Referring to the ESO-ESMO Consensus of 2014 the Applicant describes the benefit of the different therapeutic approach according to the patients characteristics as follows:

**HR Positive/HER2 Negative tumors**

In general the recommendations reported in the application regarding hormone therapy are endorsed.
For postmenopausal women (either natural, surgical, or chemical) can be treated with either tamoxifen or an aromatase inhibitor. If they were on one of these agents at the time of development of metastatic disease, they should be treated with the other agent. Treatment should continue until there is clear evidence of tumor progression, at which time the patient should be converted to the other agent (from tamoxifen to an aromatase inhibitor or vice versa). The 2 available aromatase inhibitors have equal efficacy. Stable disease is an indication to continue hormone therapy.

This reviewer recognizes that all available aromatase inhibitors have equal efficacy in metastatic breast cancer. However, also in the light of their limited added clinical benefit with respect to tamoxifen, only one active aromatase inhibitor should be added to the EML, possibly the cheapest.

In addition, while the recommendation about the shift from tamoxifen to aromatase inhibitor is agreeable, the vice versa process is not apparently supported by evidence.

A couple of further statements made this reviewer wonder that are as follows.

One first questions regards whether single agent or combined chemotherapy should be used. The Cochrane SR by Carrick S et al (2009) including 43 trials 9742 women, 55% of whom were receiving first-line treatment for metastatic disease showed a statistically significant difference in overall survival favoring the combination regimens (HR 0.88, 95% CI 0.83-0.93, p<0.00001) at the cost of statistically significant detrimental effect on white cell count, increased alopecia and nausea and vomiting.

However, while the review by Carrick et al tested the benefit of two agents given in combination compared to a single agent, it did not address the benefit of two agents given in combination versus the same drugs given as sequential monotherapy. This question was addressed by a subsequent Cochrane SR (Dear RF et al. 2013). This SR has shown that sequential single agent chemotherapy has a positive effect on progression-free survival, whereas combination chemotherapy has a higher response rate and a higher risk of febrile neutropenia in metastatic breast cancer. There was no difference in overall survival time between these treatment strategies. In particular, there was no difference in survival according to the schema of chemotherapy (giving chemotherapy on disease progression or after a set number of cycles) or according to the line of chemotherapy (first-line versus second- or third-line).

This review by Dear et al. supports the recommendations by international guidelines (as the ESO-ESMO Consensus of 2014 mentioned in the application) to use sequential monotherapy unless there is rapid disease progression. The statement highlighted above should possibly be rephrased (“sequential single agent chemotherapy”) in order to reflect this concept better.
The other question regards the suggestion to treat patients developing metastases with chemotherapeutic agents other than those used in the adjuvant setting. The recommendation is sound, but it would be useful to clarify that it is based on empirical evidence.

**HR Positive/HER2 Positive tumors**

In general the recommendations reported in the application are endorsed. This reviewer wonders what is the evidence supporting the concomitant use of vinorelbine and trastuzumab. No RCT or SR are reported in the Cochrane Library.

This reviewer also wonders whether the interim results of the CLEOPATRA study which is mentioned in the application should be considered with regard to the possible addition of pertuzumab to trastuzumab and a taxane.

Indeed, a second interim analysis of overall mortality in the CLEOPATRA study (Lancet Oncol 2013; 14:461–71) has been committed by the EMA and performed when about 2/3 of the pre-specified total number of deaths for the final analysis had occurred. This sponsor-driven trial is comparing the efficacy and safety of pertuzumab, trastuzumab, and docetaxel Vs. placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. The number of deaths among patients assigned to the placebo group was higher than that among individuals allocated to the pertuzumab group (154 [38%] of 406 Vs. 113 [28%] of 402; hazard ratio 0.66, 95% CI 0.52–0.84; p=0.0008).

However, this reviewer concurs with the Applicant that pertuzumab should not be included in the EML, since the present findings are from an interim analysis of a single sponsor-driven trial.

**Addendum:** in the meantime, the N Engl J Med of February 15, 2015 has reported the final results of the CLEOPATRA study which were in line with those of the previous interim analyses. Deaths were reported in 168 of 402 patients (41.8%) in the pertuzumab group and in 221 of 406 patients (54.4%) in the control group (HR favoring the pertuzumab group, 0.68; 95% CI, 0.56 to 0.84; P<0.001). The median overall survival was 56.5 months (95% CI, 49.3 to not reached) in the group receiving the pertuzumab combination, as compared with 40.8 months
(95% CI, 35.8 to 48.3) in the group receiving the placebo combination (HR favoring the pertuzumab group, 0.68; 95% CI, 0.56 to 0.84; P<0.001), a difference of 15.7 months. (N Engl J Med 2015;372:724-34. DOI: 10.1056/NEJMoa1413513).

Interestingly enough, only a small proportion (about 10%) of the study population have undergone adjuvant treatment with trastuzumab in the CLEOPATRA study. On one side this may limit the external validity of the trial results which would be hardly applicable in the current practice where most patients are treated with trastuzumab nowadays. On the other hand this apparent shortcoming may ensure a better transferability of the CLEOPATRA results in disadvantaged settings where trastuzumab may have not fully been adopted.

**HR Negative/HER2 Positive tumors**
It is agreed that hormone therapy is not indicated and trastuzumab chemotherapy combinations as described in the section regarding HR Positive/HER2 Positive tumors are indicated.

**HR Negative/HER2 Negative tumors**
It is agreed that hormone therapies and trastuzumab containing regimens are not indicated for these patients. As discussed in the section regarding “HR positive/HER2 negative patients” it might be clearer to state that “Sequential single agent chemotherapy should be utilized, unless there is need for rapid control of disease”

**Chemotherapy regimens**
The Applicant states that the choice of chemotherapeutic agents is arbitrary, and there are no data to suggest that initial treatment with one versus another is more efficacious. This reviewer believes that it would be useful to give some information on the evidence backing the proposed regimens which are as follows:

1. Non trastuzumab regimens for HER2 negative patients (and HER2 positive if trastuzumab is not available): doxorubicin + paclitaxel.
2. Trastuzumab-based regimens for HER2 positive patients: trastuzumab + plactitaxel (or docetaxel).
3. Single-agent chemotherapy for HER2 negative patients: capecitabine or vinorelbine or gemcitabine or cyclophosphamide.

This reviewer suggests to

- select one taxane only on the basis of its better cost-effectiveness, paclitaxel being the first option;
- provide evidence of the efficacy of capecitabine, vinorelbine, and gemcitabine which reportedly “have all been shown to have activity” for patients with metastatic breast cancer;
- provide a rationale to select option 3 instead of 1, and option 4 instead of 2.

There appears to be limited experimental evidence supporting the inclusion of capecitabine, vinorelbine, and gemcitabine. This reviewer could find the following information.

A systematic review by Oostendorp et al. (2011) assessing the efficacy and safety of palliative single-agent chemotherapy drugs - capecitabine, vinorelbine, gemcitabine, and liposomal
doxorubicin - in patients with advanced breast cancer pretreated with anthracyclines and taxanes found that rates of disease control differed significantly between agents favoring capecitabine and vinorelbine, which might be relevant to the quality of life of patients. The authors recognized the several limitations of their review and concluded that more evidence on the respective efficacy and safety of these agents should be assessed in comparative RCTs.

**Capecitabine:** the Cochrane Library only reports one phase III trial of neoadjuvant docetaxel-capecitabine versus doxorubicin-cyclophosphamide ([http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011220/abstract](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011220/abstract)).

**Vinorelbine:** the Cochrane Library reports the following limited information:
- **Single-agent vinorelbine.**
  One RCT with 179 women found that single-agent vinorelbine increased survival compared with melphalan: median survival 35 weeks with vinorelbine Vs. 31 weeks with melphalan (P=0.03); 1-year survival rates 35.7% and 21.7%, respectively (P-value not reported).
  Another trial (n=98) found no survival benefit over 5-FU plus leucovorin, with or without mitoxantrone.
  Data pooled from one phase III RCT and 8 phase II case series found that 24% of women responded to treatment using single-agent vinorelbine (95% CI: 20, 28). In anthracycline-resistant disease, the pooled response rate was 19% (95% CI: 14, 24).
- **Combined therapy.**
  One RCT in women treated with doxorubicin, with or without vinorelbine (n=303; 289 assessable), found no significant difference in median survival, response rate, or duration of response.
  Another RCT (N. not reported) compared vinorelbine plus doxorubicin with 5-FU plus doxorubicin plus cyclophosphamide (FAC). Treatment response was 76% for the vinorelbine group versus 85% for the FAC group (P-value not reported). The duration of follow-up was too short for survival analysis.

**Gemcitabine:** a meta-analysis of 9 RCTs (2651 patients) reports that compared with gemcitabine-free chemotherapy, gemcitabine-based therapy demonstrated no improvement in terms of ORR (HR 1.09, 95% CI 0.73-1.62; P = 0.67), TTP (HR 0.91, 95% CI 0.72-1.15; P = 0.44) and OS (HR 1.05, 95% CI 0.88-1.25; P = 0.60). The rates of grade 3 and 4 anemia (HR 2.02, 95% CI 1.35-3.02; P = 0.006), neutropenia (HR 2.33, 95% CI 1.37-3.63; P = 0.01), and thrombocytopenia (HR 8.31, 95% CI 5.00-13.82; P < 0.0001) were significantly higher in the gemcitabine-based arm. The authors concluded that gemcitabine-based chemotherapy was as effective as gemcitabine-free chemotherapy in patients with metastatic breast cancer with increased hematological toxicity. (Li W, et al. Current Medical Research and Opinion.2013;29:1443-52)

(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 ☑ refers to the 1st Q

No ☐
The application carefully reports common AEs associated with the use of taxanes (alopecia, neutropenia, fever and infection, and neuropathy), paclitaxel and trastuzumab (infusion reactions), tamoxifen (hot flashes, mood changes, and rarely thromboembolic disease and endometrial cancer), aromatase inhibitors (hot flashes, mood changes, musculoskeletal complaints and bone loss), vinorelbine (neutropenia and granulocytopenia), capecitabine (hand-foot syndrome), gemcitabine (thrombocytopenia, leukopenia and hepatopathy).

Among serious AEs the application reports cardiotoxicity associated with anthracyclines and/or trastuzumab; bone marrow damage, myelodysplastic syndrome and acute leukemia associated with the use of doxorubicin; and diarrhea associated with the use of capecitabine.

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 ☐

Ultrasound-guided needle biopsy (or incisional biopsy whenever needle biopsy is not technically feasible) is useful 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 to reveal metastases and their extent. 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.

See also section (8).

(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 the medicines that are proposed for the EML in this application, i.e. vinorelbine, capecitabine, gemcitabine,
trastuzumab, anastrozole (as a class agent including other aromatase inhibitors – letrozole and exemestane)

(7) Comment briefly on issues regarding cost and affordability of treatment.

The application does not address this issue. However, the cost of most current anti-cancer medicines are hardly affordable in general and even more so in disadvantaged settings. Eligibility of anti-cancers to the EML should also be considered in this perspective.

(8) Any additional comments on the application?

There is increasing evidence of the heterogeneity within the primary tumor and between the primary tumor and its metastasis. Intratumoral heterogeneity of HER2 gene amplification has been well documented and represents subclonal diversity within the tumor (Vance GH et al. Arch Pathol Lab Med.2009). HR and HER-2 expression in primary breast tumors frequently differs from that of paired metastases too (Ibrahim T, et al. Oncology 2013). This may have important implications in the diagnosis and appropriate treatment of breast cancer, including the need for multiple tumor-biopsy sampling and for re-challenges over time, which may further challenge the affordability in disadvantaged settings.

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

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

This reviewer wonders about the opportunity to include

- all the third generation of aromatase inhibitors: since they are reportedly equally effective, the cheaper should suffice;
- vinorelbine, capecitabine, gemcitabine because of the lack of evidence of their efficacy and safety and of their place in therapy with respect to the medicines and regimens adopted in the EML.

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