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

Yes ☒ No ☐

Please provide brief details:

Multiple myeloma represents about 1.8% of all malignancies and more than 10% of haematological malignancies. The incidence is about 6/100,000/year with geographic and racial variations. It is a disease of the elderly with a median age of 70 and therefore its incidence is increasing because of the demographic evolution. Overall there might be almost 200,000 cases per year worldwide now.

In many cases multiple myeloma (MM) is preceded by a precursor stage called monoclonal gammopathy of undetermined significance (M-GUS), which often, but not always, will evolve to a symptomatic MM. Overt and symptomatic MM is often preceded by a state called smouldering myeloma (in contrast to M-GUS there is not only a gammopathy but also bone marrow involvement), which is generally not treated, although lately based on a definition of high risks genetic groups, some authors are advocating an earlier begin of the treatment. The borders between smouldering myeloma not requiring treatment and of MM are therefore increasingly difficult to define. MM which requires treatment is characterized by an important M-gradient; an important bone marrow involvement with neoplastic plasma cells; often, but not always, bone lesions; general symptoms; impairment of blood values; and (rather rarely) renal insufficiency.

The treatment of MM has changed dramatically in the past decades with the introduction of new drugs into therapeutic strategies both in the frontline and relapse settings.

Together we have at least 6 different classes of agents (alkylators, steroids, proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors and monoclonal antibodies). They can be combined in doublet and triplet regimens and used together with high-dose therapy and autologous stem cell transplantation (ASCT), the latter modality having been introduced into the treatment of MM already about 20 years ago.

In the last 15 years, overall survival has at least doubled and median overall survival now approaches 6-10 years depending on the age and on the subgroup at diagnosis. This very significant improvement is not attributable to one sole drug, but to the general approach, including mainly the use of the drugs, which are here discussed for inclusion in the EML. The therapeutic question today is whether with the addition of even more drugs in first line (mainly monoclonal antibodies) it will be
soon possible to avoid ASCT. Another unresolved question is whether maintenance treatment is always necessary and if yes, for how long.

(2) Have all important studies/evidence of which you are aware been included in the application?
  Yes ☒ No ☐

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
  Yes ☒ No ☐

(a) It should first be noted that the Melphalan, which is not currently in the EML, should be added to the medicines which are essential for the treatment of MM, since this drug historically represents the backbone of the frontline treatment of MM and is still used in some patients and mainly in LMICs because of the limited cost, although not always available!

The use of the proposed medicines is intended either as part of pre-ASCT treatment in fit patients or as an alternative treatment in patients who are ineligible for ASCT, either because of age, general conditions or unavailability of this treatment modality. There are very many trials using various combinations of this biologic agent which have shown a substantive impact starting with comparison Bortezomib-Melphalan/Prednisone to Melphalan-Prednisone (this latter one having been the standard treatment in the past).

Since ASCT is standing alone the most efficacious approach, in many trials it has had a confounding impact on the definition of the advantage of adding after or before transplant these biologic agents. Therefore a benefit of these agents, which are discussed here for introduction in the EML, has been more clearly defined as being very substantive and an overall gain in OS (very significant) in the setting of ASCT ineligible patients. Similar findings have been noted for various combinations of Bortezomib, Lenalidomide, Thalidomide combined with Dexamethasone and Doxorubicin. The differences among these combinations are more related to the conditions of the patients and to the expected side effects than to the outcome as such. So thrombopenia is much more prominent with Bortezomib (which is however the drug able to produce more rapidly a positive outcome: e.g. in impending renal impairment). Bortezomib and Thalidomide are neurotoxic, which is not the case of Lenalidomide (Thalidomide derivative), whereby Lenalidomide might cause general symptoms, neutropenia, malaise. All these aspects are well described in the present application.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:
Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

(Yes ☑) No ☐

Please provide brief details:
These are not very new drugs, therefore there is a lot of experience with their use, as a single agent and/or in combination therapy. It should be considered that multiple myeloma is not a neoplasia, which can be treated by physicians, who have not at least some experience with this disease, hemato-oncology in particular and oncology in general. The side effects of the drugs are not insignificant, but not particularly worrisome. Thrombocytopenia (Bortezomib) can be controlled by adapting the dosage; neurotoxicity by Thalidomide necessitates careful evaluation, but is generally not worrisome. Lenalidomide as a pleiotropic drug is somewhat more tricky, so that in general it is advised to start with a lower dosage than the one which is to be used on a long term treatment. Overall the side effects of these drugs require less specific knowledge that the experience which is necessary to manage the treatment of MM (when to start? How to evaluate? How long to treat?).

Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).
The overall risk to benefit ratio is clearly in favour of the benefit, taking into account the fact that with these treatments the overall survival has improved very significantly and that the side effects can be generally evaluated as being rather moderate and manageable.

ADDITIONAL CONSIDERATIONS:

Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☑ No ☐

Please provide brief details:
As already stated in the previous points, special requirements on training are more needed to be able to carry out properly the diagnosis, the treatment and the overall management of patients with MM than specifically related to the drugs. Mainly in LMICs often there is a lack of sufficient knowledge and experience, at least in some countries, in that respect. This is true for the whole sector of hematopathology as it has been recognized very often by many assessments.

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

Yes ☐ No ☑
Please provide brief details:

(8) **Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?**

   Yes ☐  No ☐

Please provide brief details:
Bortezomib is already included in the EML for the treatment of some subsets of lymphomas.

(9) **Please comment briefly on issues regarding cost and affordability of this medicine.**

The most expensive part of the current treatment of MM is ASCT. The medicines proposed are overall cost-effective, taking into account the gain of overall survival. They are already available or will become available soon as generics.

(10) **Any additional comments?**

(11) **Please frame the decisions and recommendations that the Expert Committee could make.**

The medicines proposed have manageable toxicity and have contributed significantly to the important improvement in the overall survival of patients with MM. For that reason, they should therefore be included in the EML.

(12) **References (if required)**