A.9	Daratumumab – multiple myeloma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Daratumumab is a monoclonal antibody, anti-CD38, a marker highly expressed by malignant plasma cells. Hence, Daratumumab is a target therapy that induces tumor cell death through multiple immune-mediated mechanisms of action, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), as well as through apoptosis, in which a series of molecular steps in a cell lead to its death. Daratumumab is being evaluated by several multicentric-Randomized Clinical Trials (RCTs) based on MM patients' outcomes, the overall survival and the progression-free survival (endpoints), comparing Daratumumab- treated group versus control groups, in different indications. Daratumumab (Darzalex©) is tested in combination with Bortezomib (Velcade©), Melphalan and prednisone (D-VMP), or in combination with Velcade, lenalidomide and dexamethasone, in newly diagnosed MM patients, eligible or not to autologous transplantation. Daratumumab is also tested, in combination with Carfilzomib and dexamethasone or with Bortezomib and dexamethasone or with lenalidomide and dexamethasone in relapsed or refractory patients after a treatment including at least a proteasome inhibitor and an immunomodulatory agent.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Transplant ineligible newly diagnosed MM patients RCTs: (MAIA, ALCYONE) Overall Survival (OS): Follow-up time 37 months (Median survival not reached). 85 (23%) versus 103 patients (27.9%) have died in the Daratumumab versus the control group; (hazard ratio HR 0,67- 95%CI 0,5-0,85) [Moderate evidence]. Progression free survival increased in the Daratumumab versus the control group [Moderate evidence]. Transplant eligible newly diagnosed MM patients

	RCTs: CASSIOPEIA, GRIFFIN OS, Follow-up time 18 months (Median survival not reached): Treatment with daratumumab may increase overall survival when compared to treatment without daratumumab (HR 0.52- 95%CI 0.33 to 0.82) [low-certainty evidence]. Progression free survival (surrogate endpoint): Treatment with daratumumab may increase progression-free survival when compared to treatment without daratumumab (HR 0.49- 95%CI 0.36 to 0.68) [very low-certainty evidence]. Relapsed or refractory Multiple myeloma RCTs: LEPUS, POLLUX, CANDOR, CASTOR OS: Follow-up time depending on the RCT (Randomized Clinical Trial): from 8 to 17 months (Median survival not reached); Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab (HR 0.62, 95%CI 0.49 to 0.79) [moderate-certainty evidence]. Progression free survival: Treatment with daratumumab may increase progression-free survival when compared to treatment without daratumumab (HR 0.40, 95% CI 0.29 to 0.56) [low-certainty evidence]. *Quality of life (QoL) has been assessed in different RCT and reported in the present document; 10 points increase in QoL has been found in favor of Daratumumab group with moderate to low certainty depending on the RCT and on the indication of the drug. The design of the RCTs are open label that may, as mentioned in the proposal, bias the assessment of patient quality of life. The points of bias of the studies that impacted the certainty of the results are mainly related to the design of RCT, open label, the high number of patients drop out mainly explained by death, the short follow-up time…. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? There was no report of efficacy in different groups in the present proposal.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Haematological parameters and the side effect, respiratory Infectious diseases require monitoring and reassessment to continue or not the Daratumumab treatment.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	There is moderate evidence of a positive overall benefit/risk considering: 1/ Certain limitations in the design of the RCT 2/ the immaturity of the overall survival data 3/ the side effects associated with the medicine. An overall positive benefit/risk by adding daratumumab to Bortezomib, Melphalan, and prednisone (VMP) or to Lenalidomide and dexamethasone, in Transplant ineligible newly diagnosed MM patients, or in Refractory MM patients who have received at least one prior therapy, or in monotherapy for refractory patients that have received at least three prior lines of therapy including a proteasome inhibitor and immunomodulatory agents are the indications that may present a positive benefit/ risk ratio
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of the evidence for the treatment is moderate.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Follow up in case of infections.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Based on the costs as reported in studies from USA, UK, cited in the present proposal for the inclusion of Daratumumab in the WHO model list of essential medicines for the treatment of MM, the Incremental Cost-Effectiveness Ratio (ICER) was highly variable depending on the indication and on the time horizon considered in the study. The economic evaluation was mainly studied for the indication: refractory MM patients. A range of ICER from 50000 US$ to 1.369.000 US$ has been reported. The high cost is due to the high cost of the acquisition of Daratumumab. A concern of accessibility would certainly be raised for many countries, particularly for low and middle-income countries.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	When we consult the cost-effectiveness evaluation completed by HAS (Haute Authorite de Sante, France). It was achieved for refractory MM patients (extraction of input parameters from the RCT POLLUX and CASTOR). An ICER of the association of daratumumab to lenalidomide and dexamethasone was estimated to 531000E/QALY (time horizon 30 years), limiting the efficiency of Daratumumab (Ref1). Daratumumab was licensed in Europe, and regulatory agencies of European countries were favourable for its reimbursement, as in France, in the specific indication: newly diagnosed multiple myeloma ineligible for autologous transplantation, in combination with VMP-protocol, (Ref2, Ref3). The economic evaluation is still ongoing in many European countries Belgium, Switzerland (Ref4), and may not be accepted in other countries. Routine access through the country's national healthcare provider was not granted in UK. (Ref5) The high cost of the drug and the moderate evidence of the improvement of patients' OS when adding Daratumumab to pre-existing protocols, may hamper the approval/ grant and the access to Daratumumab, or limiting its indications. An overall positive benefit/risk by adding daratumumab to Bortezomib, Melphalan, and prednisone (VMP) or to Lenalidomide and dexamethasone, in Transplant ineligible newly diagnosed MM patients, or in Refractory MM patients who have received at least one prior therapy, or in monotherapy for refractory patients that have received at least three prior lines of therapy including a proteasome inhibitor and immunomodulatory agents are the indications that may present a positive benefit/ risk ratio
References (if required)	Ref1. https://www.has-sante.fr/upload/docs/application/pdf/2019-07/darzalex_12122017_avis_efficience.pdf Ref2. https://www.mpeurope.org/2018/09/04/daratumumab-receive-european-license-for-use-in-newly-diagnosed-myeloma/ Ref3. https://www.has-sante.fr/jcms/p_3183497/fr/darzalex-daratumumab Ref4. https://www.has-sante.fr/upload/docs/evamed/CT-18404_DARZALEX_1eL_non_eligibles_PIC_REEV_AvisDef_CT18404.pdf Ref5. https://www.thepharmaletter.com/article/j-j-scores-partial-reimbursement-win-for-darzalex-combo-in-the-uk