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: Multiple myeloma is the second most common hematological malignancy and is increasing in incidence in many regions of the world. Treatment is non-curative for the great majority of patients. Major unmet needs are for improvements in overall survival (especially in poor prognosis subgroups), improvements in overall quality of life during ongoing therapy, and reduction in toxicity of long term therapies.
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 against CD38, an antigen widely expressed by myeloma cells. It is proposed to be added to standard combination therapy for first line treatment or later line treatments for patients with symptomatic multiple myeloma. These standard therapies include drugs already included on the EML for myeloma, including dexamethasone, bortezomib, lenalidomide, melphalan and zoledronic acid.
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). <u>Overall survival</u> The **addition of daratumumab to standard combination therapy increases survival in individual trials in the following settings, but with immature follow up (median survivals not reached)**: - first line, non-transplant eligible (hazard ratio [HR] 0.67, 95% confidence interval (CI) 0.5 to 0.85) - first line, transplant eligible (HR 0.52, 95% CI 0.33 to 0.82) - relapsed/refractory (HR 0.62, 95% CI 0.49 to 0.79) moderate certainty *These **reductions in risk of death are clinically important** and are of a magnitude consistent with improvements in survival observed previously for other drugs listed on the EML for treatment of myeloma - bortezomib and lenalidomide.* <u>Progression-free survival</u> Consistent with these findings of early improvement in survival when daratumumab is

	added to standard therapy, the review identified that in meta-analysis of PFS as a surrogate endpoints, **daratumumab use increased PFS** in: not reached): - first line, non-transplant eligible (HR 0.48, 95% CI 0.36 to 0.63) EMBO-MCBS 4/4 - first line, transplant eligible (HR 0.49, 95% CI 0.36 to 0.68) immature, v low certainty - relapsed/refractory (HR 0.4, 95% CI 0.29 to 0.56) EMBO-MCBS 3/4 <u>Quality of life</u> Similarly, when considering quality of life, there was **evidence of meaningful improvement for more patients receiving daratumumab**: - first line, non-transplant eligible (risk ratio [R/R] for gain >10 points 1.13, 95% CI 1.13 to 1.23) - first line, transplant eligible (RR 1.07, 95% CI 0.91 to 1.24) low certainty - relapsed/refractory (RR 1.07, 95% CI 01.07 to 1.22) low certainty ***Collectively, these data strongly suggest that addition of daratumumab to conventional therapy provides a significant advance in treatment efficacy for patients with multiple myeloma, and that the magnitude of that advance is substantial and very clinically important*.** Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Not provided
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: As expected, the **addition of daratumumab to conventional therapy overall increases toxicity of treatment modestly in meta-analyses of trials in the three settings**: First line, non-transplant eligible: - Adverse events (AEs) ≥3: RR 1.05, 95%CI 1.0 - 1.11 high certainty - Serious AEs: RR 1.14, 95%CI 0.86 - 1.51 v low certainty - Infections: RR 1.42, 95% CI 1.19 to 1.70 high certainty - Pneumonia: RR 2.16, 95% CI 1.15 to 4.06 moderate certainty First line, transplant eligible: - AEs ≥3: RR 1.06, 95%CI 1.0 - 1.13 high certainty - Serious AEs *may decrease*: RR 0.91, 95%CI 0.73 - 1.14 low certainty - Infections: RR 1.12, 95% CI 0.90 to 1.39 moderate certainty - Pneumonia *likely unchanged*: RR 1.05, 95% CI 0.60 to 1.84 moderate certainty Relapsed / refractory myeloma: - AEs ≥3: RR 1.17, 95%CI 1.04 - 1.31 moderate certainty

	- Serious AEs: RR 1.21, 95%CI 1.09 - 1.35 moderate certainty - Infections: not poolable, but clear trends in both trials for increase - Pneumonia: RR 1.28, 95% CI 0.86 to 41.90 low certainty
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Infections are clinically important toxicities which are very likely increased when daratumumab is added to conventional therapy.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	**The multiple trial data across key clinical scenarios - first line and relapsed - indicate a highly favourable benefit to risk ratio, with substantial improvements in survival, progression-free survival and quality of life, at the expense of modest additional toxicity, including infections.**
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The quality of evidence is judged as high overall given the number of trials and the consistency of their findings across settings. This consistency mitigates against some imperfections in quality of study design for individual trials. It is anticipated that the certainty of evidence should increase as the trials mature.
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: This drug can interfere with blood group typing, and specialized transfusion laboratory practices are required as a routine for its safe use. These are transferable to most countries, but do add additional costs (albeit minor compared to drug costs).
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: The drug is widely approved in high resource countries, as summarised in the application.
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: Daratumumab is recommended by multiple treatment guidelines in Europe, USA and Asia.

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Daratumumab is a very high cost medicine that remains under patent. As outlined in the application, the principle incremental cost of therapy in all settings relates to acquisition costs for daratumumab, and this varies according to the setting (ie monotherapy as last line, in combination first or subsequent lines), the partner drug(s) ie bortezomib or lenalidomide, and the comparator (standard care without daratumumab or an alternative daratumumab-containing regimen). Perhaps the most relevant cost-effectiveness analysis was the NICE HTA which related to a comparison in second line setting of a standard therapy (bortezomib and dexamethasone) and the same therapy with daratumumab. With a time horizon of 30 years, the ICER was GB£ 93,061; with a time horizon of 10 years, the ICER was GB£ 134,555. Daratumumab is highly effective but extremely expensive. Without availability of alternative agents (ie biosimilars, other agents targeting CD38) to drive competition, or pragmatic drug pricing and significant subsidies, the current cost of daratumumab is prohibitive in many countries and unlikely sustainable in the majority of low and middle income countries in the public sector. Other unanswered considerations that impact cost include: - the most cost-effective duration of therapy in first or other lines? - whether repeated use is similarly efficacious and whether this influences cost-effectiveness?
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.	Recommend against inclusion in 2021, but that daratumumab is reconsidered when the trial data are more mature. It is highly probable that the magnitude of benefit from addition of daratumumab to standard therapy warrants its inclusion on EML at some point in the future. Cost considerations are likely to be the primary barrier to its use in countries with limited health care resources.
References (if required)	