I.10	Cisplatin and Carboplatin as medicines for early- and advanced-stage head and neck cancers
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: As noted in the submission, head and neck cancers encompass many different tumors, including oral cavity and oropharyngeal cancers. Their incidence shows a significant geographical variation, with a higher incidence in South Asia and a lower incidence in Western Sub-Saharan Africa and Andean Latin America. Overall, the 5-year survival is around 67%. Although it largely depends on the location of the cancer and its stage. Together, they account for a significant number of new cases and deaths worldwide every year - with 878,348 new cases and 467,125 deaths estimated worldwide in 2020. These numbers highlight the importance of addressing these cancers even without taking into consideration the morbidity that invariably accompanies their presentation and occur during their management.
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.	Comments: The report that was submitted updates a previous application addressing the use of platinum-based chemotherapy for early- and advanced-stage head and neck cancers. Both cisplatin and carboplatin are already included in the WHO Model List of Essential Medicines for cancer. In that regard this is not a request for inclusion of a new medicine but a proposal to ratify their use in early and advanced stage head and neck cancers.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable Comments: While the submission has been diligent in its review in fact the overwhelming amount of reviewed data is based on cisplatin and not on carboplatin. This is noted in the submission - “Six trials assessed the effect of cisplatin, while two evaluated carboplatin.” Additionally, one of the two carboplatin trials also included 5-fluorouracil in the chemotherapy regimen. Thus, the data analysis is primarily driven by cisplatin
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Comments: As noted above the published data is heavily weighted to cisplatin over carboplatin although the application seeks endorsement for both cisplatin and carboplatin – the carboplatin endorsement assumes cisplatin and carboplatin are comparable/indistinguishable and in fact they are not. Comparisons in several diseases including the closely related NSCLC have achieved divergent results and led to divergent conclusions. These differences in results and conclusions are likely explained in part or in their entirety by differences in how the drugs are dosed – cisplatin usually by BSA (body surface area) and carboplatin according to AUC (area under the curve). A recent meta-analysis of 5 studies (491 patients) evaluated carboplatin versus cisplatin in squamous head and neck cancer. Overall response trended to cisplatin but was not statistically significant (RR 0.97; 95% CI 0.89 to 1.05). There was little difference between agents for time to progression or locoregional free survival.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: From the systematic reviews identified 26 trials were found that reported data on adverse effects. The submission observed that the addition cisplatin or carboplatin to radiotherapy could result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34) a relative risk that achieved statistical significance and is statistically significant although described as “low certainty evidence”.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: In the safety analysis the submission notes that the addition cisplatin or carboplatin to radiotherapy could result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34). The most common adverse events were mucositis, skin toxicity, dysphagia and stomatitis. The latter must be managed aggressively they could lead to a reduction in the radiation therapy dose administered and compromise efficacy.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The analysis of eight randomized trails (n = 2325) showed that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival by 2 months (HR 0.95, 95% CI 0.80-1.12) a result that is not statistically meaningful and at 2-months it must be predictably that robust to argue it is clinically meaningful a challenge in the real-world of oncology. In the safety analysis the submission notes that the addition cisplatin or carboplatin to radiotherapy could result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34). Both results are described as “low certainty evidence” although statistically the efficacy result is not valid whereas the toxicity outcomes are. One must assess the overall benefit to risk ratio of adding cisplatin or carboplatin to radiation therapy in head and neck cancer as uncertain.
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 is not as robust as it should be in part since it emanates from a diverse group of studies that have been analysed together in a meta-analysis. The data combines studies with two different platinum compounds and in one case 5-gluoruracil is administered in addition to cisplatin. Furthermore, as noted, not all studies were blinded. As regards efficacy, the addition of cisplatin or carboplatin to radiotherapy increased overall survival by 2 months (HR 0.95, 95% CI 0.80-1.12) a result that is not statistically meaningful. In the safety analysis the submission notes that the addition cisplatin or carboplatin to radiotherapy could result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34). Both results were described as “low certainty evidence” although statistically the efficacy result is not valid whereas the toxicity outcomes are.
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: There are no special requirements that are not part of standard of care nor that would not be available where the proposed therapies would be administered.
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.	Both cisplatin and carboplatin are drugs that are widely available as generic formulations and can be considered accessible and affordable.
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.	The submission can be considered for approval. Data on efficacy has been carefully sought out but it must be acknowledged the benefit of adding chemotherapy to radiotherapy in the management of head and neck cancers is at best marginal and possibly not existent. As the submission notes, seventeen systematic reviews were found without a new trial since the last application. In their summary of the data regarding the use of platinum-based chemotherapy they note in almost all trials cisplatin was used as a single chemotherapy agent. Most of the trials were conducted in individuals with locally advanced disease. Their analysis of eight randomized trails (n = 2325) showed that the addition of cisplatin or carboplatin to radiotherapy may increase overall survival by 2 months (HR 0.95, 95% CI 0.80-1.12) a result that is described as “low certainty evidence” but in fact is not statistically meaningful and at 2-months it must be predictably that robust to argue it is clinically meaningful. An approval for this indication must not be seen as an endorsement of the use of chemoradiotherapy in all patients with head and neck cancer, but only that it can be considered and exclusively in individuals who are likely to tolerate the combined chemoradiotherapy well. Finally In the safety analysis the submission notes that the addition cisplatin or carboplatin to radiotherapy could result in 52 more patients with adverse events per 1000 treated (RR 1.16, 95% CI 1.01-1.34). The most common adverse events were mucositis, skin toxicity, dysphagia and stomatitis. The latter it must be noted are the side effects that could lead to a reduction in the radiation therapy dose administered. One must be cognizant that if such toxicity occurs and the administered doses of radiation are reduced then the outcome may not only not be superior but may actually be inferior.
References (if required)	