A.2	Alfacalcidol and calcitriol – disorders of bone and calcium metabolism – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The body of evidence available is still uncertain for most clinically important endpoints; however, the use of calcitriol and alfacalcidol are more likely to have desirable effects in the relevant populations with fewer undesirable effects. Monitoring and conditions will need to apply since there still the possible of adverse events such as hypercalcemia, and applicability and implementation issues need to be addressed such as the administration in special populations (children, cardiovascular disease, etc.)
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Chronic kidney disease and the other (alas less common but relevant) conditions such as x-linked hypophosphatemic rickets, vitamin D dependent rickets, and hypoparathyroidism, together represent a group with a relevant need for and that will benefit from including the proposed medicines in the essential lists.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The application submits three guidelines providing conditional recommendations on both medications for the populations addressed in this submission. Further published systematic reviews and overviews of the evidence for CKD [Christodolou 2021] denotes that calcitriol and alfacalcidol likely results in benefits for CKD patients in terms of PTH concentrations and increase in fibroblast growth factor 23, both indirect measures of more important clinical outcomes (e.g., fractures, health-related quality of life). The body of evidence is uncertain due to risk of bias, indirectness when assessing patient important outcomes, inconsistencies, and imprecision.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The same bodies of evidence mentioned for efficacy outcomes addressed the possible harms with these medications. It is important to note that the use of calcitriol and alfacalcidol is likely to produce little to no important harms, such as hypercalcemia (found in only one of 12 RCTs in a recent systematic review and overview of guidelines [Christodolou 2021]).

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Hypercalcemia could be rare but also can be bothersome and require specific interventions.
Are there any special requirements for the safe, effective, and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: As mentioned above, special monitoring for hypercalcemia might be required in some cases such as children, patients with cardiovascular disease, under digitalis treatment, etc.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Calcitriol and alfacalcidol are relatively inexpensive medications. Calcitriol budget impact analysis has an estimated 1-year cost per patient of 63.88 USD [Manjarres 2016]
Are there 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? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Recommendations in WHO guidelines were not found