| I.9 | Zoledronic acid – osteogenesis imperfecta – EML and EMLc |
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| **Draft recommendation** | ☒ Recommended<br>☐ Not recommended<br>Justification: Bisphosphonates are the primary treatment in children with moderate to severe osteogenesis imperfecta (OI). The body of evidence is of low certainty but suggest that zoledronic acid may reduce fracture risk in patients with OI and may have similar effects than other bisphosphonates in terms of bone density, pain, function, and HRQoL. Harms are rare and clinically manageable. Zoledronic acid is administered once or twice a year and it has a low-cost profile. Even with a low certainty body of evidence, I think the desirable effects likely outweigh the undesirable effects and represents an opportunity to fill a need in patients with this condition, especially in LMICs. |
| Does the proposed medicine address a relevant public health need? | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: Osteogenesis imperfecta is a rare disease occurring in 1 in 10,000 to 20,000 births. Most cases come from a mutation in the genes that encode for alpha 1 (COL1A1 gene) or alpha 2 (COL1A2 gene) chains of Type 1 collagen. This leads to a defect in the synthesis, structure, or processing of Type 1 collagen. Group A includes osteogenesis imperfecta Type I, II, III and IV and has an autosomal dominant transmission. Group A represents the vast majority of osteogenesis imperfecta. The prevalence and incidence data are likely to vary markedly according to the populations. |
| Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: Due to the rare nature of the disease it will be difficult to find large, randomized studies addressing the use of a relatively new intervention. Overall, the body of evidence points to a trivial to no difference between zoledronic acid and pamidronate or alendronate. Overall, the current evidence from systematic reviews suggest that bisphosphonates (all types) increase bone mineral density in children and adults. The evidence is uncertain for other outcomes such as improvement in the number of fractures and clinical status (pain, growth, function, HRQoL). When comparing zoledronic acid to other bisphosphonates, the evidence suggests that there are minimal to no differences among them, however, this body of evidence is of low to very low certainty. One recent RCT (Lv 2018) concludes that the effects in increasing bone mineral density and reducing bone resorption in children and adolescents with OI was similar between those treated with alendronate vs zoledronate, but that zoledronate was superior in reducing the clinical fracture rate. |
| Does adequate evidence exist for the safety/harms associated with the proposed medicine?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: Like the efficacy data, harms evaluated in the body of evidence presented suggest likely no meaningful difference between zoledronate and alendronate or pamidronate. One recent RCT showed higher incidence of AEs in patients receiving zoledronate vs alendronate, but similar serious AEs and withdrawals due to AEs. Other studies showed similar results with similar |

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| Are there any adverse effects of concern, or that may require special monitoring? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Risks are similar in children and adults. The most important difference is that osteonecrosis of the jaw, a significant clinical problem associated with long-term bisphosphonate use in adults, has not been reported in the paediatric age group. Oral and esophageal ulcers are reported with the use of bisphosphonates but not with zoledronate. Other AEs are usually mild and clinically manageable. |
| Are there any special requirements for the safe, effective and appropriate use of the medicines?<br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Health professionals with experience in the management of patients with OI should be the ones administering bisphosphonates and monitoring for adverse events and other outcomes of interest. |
| Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings? | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: There is uncertainty as there are no cost effectiveness studies on bisphosphonates and OI. There are several articles on cost effectiveness of bisphosphonates on osteoporosis in adults, including a recent systematic review of existing analyses, but this is difficult to apply to osteogenesis imperfect in the paediatric age group.<br>Overall, the cost of Zoledronic acid seems low and varies by country, for example:<br>Argentina: 5 mg in 100 ml (= 270 USD)<br>India: 4 mg/ml: 2910 INR (= USD 35.21)<br>Mexico: 5 mg/100 ml: 582 pesos (= USD 30.04)<br>Canada: 4 or 5 mg/5 ml vial: 345.03 CAD (= USD 254) |
| Are there any issues regarding the registration of the medicine by national regulatory authorities?<br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: zoledronic acid is presently included in the EML for the management of cancer-related bone pain |
| Is the proposed medicine recommended for use in a current WHO guideline?<br>(refer to: https://www.who.int/publications/who-guidelines) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: |