I.9	Zoledronic acid – osteogenesis imperfecta – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: It is already in the WHO EML list; the new indication could expand the use of the medicine to other conditions.
Does the proposed medicine address a relevant public health need?	☐ Yes ☒ No ☐ Not applicable Comments: The conditions currently indicated for the proposed medicine (i.e. Osteogenesis Imperfecta) is very rare.
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: Although bisphosphonates are the most widely used agents for the treatment of osteogenesis imperfecta, yet the most reported effect is on pamidronate therapy. The proposed medicine (ZA) is the more recent and considered 10-100 times more potent. Hence it needs less frequent and shorter time in administering it compare to pamidronate. Effectiveness of ZA is proven on bone mineral density, but still inconsistent on other patient-oriented outcomes such as fracture, pain, growth, functional and quality of life.[1] However, zoledronic acid is presently included in the EML for the management of cancer-related bone pain. Small number of studies on bisphosphonate and even very few on zoledronic acid.
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: Zoledronic acid has been included in the EML since 2017 in the Complementary List of the EML "as a therapy for patients with cancer and bone metastases. Bisphosphonates are generally well tolerated in pediatric patients. Adverse effects are limited, and are predictable based on previous trials. However, it was based on very limited number of studies, and safety report was not solely on ZA. Presently contraindicated in pregnancy.

[1] Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonates therapy for osyeogenesis imperfecta. Cochrane Database Syst Rev. 2014;7:CD005088.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Adverse effects as mentioned in the application.
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: The conditions are usually managed by specialist (pediatric endocrinologists, pediatric orthopedic surgeons, and, in some countries, by general pediatricians).
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: The cost is affordable considering that it is only administered 2x/year.
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: Approved by FDA, EMA, Health Canada and Japan PMDA. Already in the WHO EML since 2017 as a therapy for patients with cancer and bone metastases, yet currently only 38 countries included it in their EML.[2]
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: No WHO guideline about the conditions where the proposed medicine is indicated.

[2] https://global.essentialmeds.org/dashboard/medicines/2062