Zoledronic acid

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

EMLc | ATC codes: M05BA08

Indication	Osteogenesis imperfecta ICD11 code: LD24.K0
INN	Zoledronic acid
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 4 mg per 5 mL in 5 mL vial ; 4 mg per 100 mL in 100 mL bottle
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Zoledronic acid
DrugBank	Zoledronic acid

Expert Committee recommendation

The Expert Committee noted that osteogenesis imperfecta is a rare genetic disease and that bisphosphonates are commonly used in the treatment of moderate-to-severe forms in children and adolescents. The Committee noted that available evidence suggests that bisphosphonates may increase bone mineral density in children and adolescents with moderate-to-severe osteogenesis imperfecta. However, the Committee considered that the benefits associated with bisphosphonates were unclear for other important outcomes including fracture risk, bone pain, physical functioning and health-related quality of life. In particular, the Committee noted that the effects of bisphosphonates in reducing fracture risk were not consistent across trials and that it was not clear to what extent fracture risk might be reduced. The Committee noted that serious harms associated with bisphosphonate treatment in osteogenesis imperfecta were rare and clinically manageable. Based on these considerations, the Expert Committee did not recommend inclusion of zoledronic acid on the EML and EMLc for the new indication of osteogenesis imperfecta.

Background

Zoledronic acid has not previously been considered for inclusion in the Model Lists for the management of osteogenesis imperfecta. Zoledronic acid has been included on the complementary list of the EML for the treatment of malignancy-related bone disease since 2017.

Public health relevance

Osteogenesis imperfecta is reported to occur in 1 in 10 000 to 20 000 births (1). Most cases result 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. Overall, there are more than 18 types of osteogenesis imperfecta (2). Osteogenesis imperfecta phenotypes I to IV have autosomal dominant transmission and account for about 95% of all cases – type I 45%, type II 10%, type III 25% and type IV 20% (3). The worldwide population frequency of type I osteogenesis imperfecta has been reported to range from 2.35 to 4.7 per 100 000. The incidence of type II osteogenesis imperfecta has been reported to range from 1 in 40 000 to 1.4 in 100 000 live births. In resource-constrained countries, less severe forms are less likely to be seen. The genetic background is also likely to play a role (3). A Swedish study found an overall prevalence of osteogenesis imperfecta type I of 7.4 in 100 000 (4). A Dutch study (674 patients with osteogenesis imperfecta across the country) showed that the life expectancy of these patients was adversely affected by the disease. The median annual incidence risk of osteogenesis imperfecta between 1992 and 2019 was 6.5 per 100 000 live births. Patients with osteogenesis imperfecta had a 2.9 times higher rate of hospitalization compared with the general Dutch population, especially in the patient group aged between 0 and 19 years, where the risk was 8.4 times higher (5).

Benefits

Bisphosphonates are indicated for the management of osteogenesis imperfecta with moderate-to-severe pain and with bone fractures that are present in infancy, childhood and adolescence. In mild cases, no benefits of bisphosphonates have been demonstrated (6). The bisphosphonate first investigated for use in severe osteogenesis imperfecta was pamidronate (7). Since then, zoledronic acid has become available and is preferred in clinical practice based on convenience and lower hospital expense: zoledronic acid only needs to be administered once or twice a year while pamidronate needs to be administered 3–4 times a year. Administration of zoledronic acid is by a 30-minute infusion, while each administration of pamidronate consists of three consecutive daily infusions of several hours. As regards outcomes and side-effects, clinicians consider both products to be equivalent. A 1-year study comparing the efficacy and safety of zoledronic acid and pamidronate showed that zoledronic acid was as safe and effective as pamidronate in promoting clinical and densiometric improvements (8). The benefits of zoledronic acid treatment for moderate and severe forms of osteogenesis imperfect include reduced bone pain, increased bone mineral density and a decrease in the number of fractures. Bone pain A cross-sectional study with 28 participants with osteogenesis imperfecta I, III and IV found that pain was present in almost all children with moderate-to-severe disease (9). This interfered with the children’s everyday lives, affected participation in various activities and was associated with reduced self-perceived health status. The authors hypothesized that pain and the ensuing decrease in physical activity might further decrease bone density and increase the risk of fractures. An observational study of the use of the bisphosphonate pamidronate in 30 children with severe osteogenesis imperfecta reported an improvement in bone pain which was associated with an improvement in mobility (7). A prospective observational study evaluated pain and quality of life in 33 children and adolescents with osteogenesis imperfecta over a single intravenous bisphosphate treatment cycle (10). Participants reported pain of mild intensity localized in several body areas (ankles, shoulders). Self-reported pain intensity after zoledronic acid infusion did not differ from before treatment at 1 week and 6 months after treatment. Participants’ parents perceived an improvement in functioning and quality of life immediately after treatment compared with before, but no significant change was reported by the participants themselves. Another prospective observational study evaluated pain and functioning in 22 children and adolescents with osteogenesis imperfecta over two bisphosphate infusion cycles (11). Participants received pamidronate (n = 16) or zoledronic acid (n = 6). Pain was assessed using a visual analogue scale and physical functioning was assessed using the Peds QL Generic Core inventory. The results showed that cyclic intravenous bisphosphonate therapy transiently reduced pain until 4 weeks postinfusion. Physical functioning scores improved 4 weeks after infusion. Both pain and physical functioning had returned to pretreatment levels by the time of the second infusion. A 2016 Cochrane systematic review (14 trials, 819 participants) evaluated the effectiveness and safety of oral and intravenous bisphosphonate therapy in increasing bone mineral density, reducing fractures and improving clinical

function in people with osteogenesis imperfecta. One trial compared intravenous bisphosphonate (pamidronate) with placebo for the outcome of bone pain in children and did not find a difference in bone pain reduction scores between the two groups. The mean difference (MD) favoured bisphosphonate treatment but was not statistically significant (MD –0.11, 95% confidence interval (CI) –0.83 to 0.61) (12). Bone mineral density The observational study using pamidronate at a standard dose of maximum 9 mg/kg a year reported a marked increase in bone mineral density over several years (7). The Cochrane systematic review included three trials comparing of intravenous bisphosphonates (neridronate or pamidronate) with placebo for changes in bone mineral density (12). Mean percentage changes from baseline in spine bone mineral density favoured bisphosphonate treatment but were not statistically significant at 6 months (MD 9.96, 95% CI –2.51 to 22.43) and 12 months (MD 14.68, 95% CI –6.08 to 35.45). Mean percentage changes (z score) in spine bone mineral density significantly favoured bisphosphonate treatment at 6 months (MD 21.59, 95% CI 5.79 to 37.39) and 12 months (MD 25.6, 95% CI 11.48 to 39.72). Mean percentage changes in total hip bone mineral density favoured bisphosphonate treatment but they were not statistically significant at 6 months (MD 6.16, 95% CI –3.57 to 15.9) and 12 months (MD 11.27, 95% CI –3.69 to 26.22). Fractures The application remarked that it was difficult to assess the data of the effects of bisphosphonates on fracture rates in patients with osteogenesis imperfecta, given that when there is a decrease in pain and an increase in mobility, a higher risk of fractures is not unexpected. The Cochrane systematic review concluded that although multiple studies reported decreases in fracture rates independently and no studies reported an increased fracture rate with bisphosphonate treatment, the effect of bisphosphonate treatment in consistently decreasing fractures was unclear (12). In the comparison of intravenous bisphosphonates versus placebo, the difference in fracture rates favoured bisphosphate treatment but was not statistically significant (risk ratio 0.53, 95% CI 0.30 to 1.06). A retrospective study assessed the effects of long-term intravenous bisphosphonate treatment during growth in 37 children with osteogenesis imperfecta who had started treatment before 5 years of age, had subsequent follow-up of at least 10 years and had received treatment for at least 6 years (13). All the children had had long-bone or vertebral compression fractures before intravenous bisphosphonate treatment was started but the number of fractures could not be determined with certainty due to lack of radiographic documentation. All the children initially received pamidronate and 30 eventually received zoledronic acid. During the observation period, the children had a median of six and five radiologically documented femur and tibia fractures, respectively. The mean rate of fracture in lower extremity long bones decreased during the first 2 years of treatment and thereafter remained stable. Visible compression fractures decreased markedly between the pretreatment and last follow-up or final (before spinal fusion) radiographs. The number of vertebral compression fractures was significantly lower ($P < 0.01$) at the time of the last bisphosphonate infusion compared with a control group of patients who were matched for age, sex and osteogenesis imperfecta type who had not received bisphosphonate treatment. An observational cohort study evaluated the effects of bisphosphonate treatment on bone mineral density and other health outcomes in type 1 osteogenesis imperfecta (14). Logistic regression modelling predicted that with bisphosphonate exposure, a 1-year increase in age would be associated with a significant decrease of 8.2% in fracture probability for preadolescent (age < 14 years) children, compared with no decrease in untreated children. An increase in lumbar spine areal bone mineral density of 0.1 g/cm2 was associated with a 10.6% decrease in scoliosis probability, compared with a 46.8% increase in the untreated group. For the same changes in age and lumbar spine areal bone mineral density in preadolescent children, bisphosphonate exposure was also associated with significantly higher mobility scores.

Harms

Several risks are associated with treatment with bisphosphonates and require monitoring (15). Risks are generally similar in children and adults. However, 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 (16). A systematic review evaluated the literature on the risk of bisphosphonate-related osteonecrosis of the jaw in children and adolescents (17). In the seven studies included, no cases of osteonecrosis of the jaw were identified. However, the authors noted weaknesses in the studies (e.g. small sample size and absence of risk factors for development of osteonecrosis of the jaw) and concluded that further studies should be conducted. Oral and oesophageal ulcerations (and potentially cancer of the oesophagus) have only been reported with oral bisphosphonates (18).

Bisphosphonates are reported to be generally well tolerated in paediatric patients and adverse effects are limited and predictable. A recent review (19) describes the following adverse events. • Acute phase reaction (so called flu-like syndrome) is observed with fever, malaise, abdominal pain, vomiting, and muscle or bone pain within 1–3 days of starting either intravenous or oral agents, and lasting a few days. • Asymptomatic hypophosphatemia, and hypomagnesaemia and hypocalcaemia causing tetany are rare and can be prevented with supplementation with calcium and vitamin D. • More serious side-effects seen in adults including uveitis and thrombocytopenia are rare in children. One case of uveitis was reported among 19 children with Langerhans cell histiocytosis treated with bisphosphonates in Japan (20) although histiocytosis itself has also been associated with uveitis (21). • Avascular necrosis of the jaw seen in adults is not seen in paediatric patients. • A severe case of respiratory distress syndrome was reported with the start of pamidronate in an infant with a history of airway disorders (22). • Osteomalacia (and marked decrease in bone pain) was seen in an adolescent with fibrous dysplasia after intravenous cyclic pamidronate therapy (23). Bisphosphonates are contraindicated during pregnancy. Bisphosphonates stay in bone for a long time. They can be released during bone remodelling. Whether this would cause problems, for instance, during pregnancy is unclear. In two infants delivered to mothers treated with bisphosphonates, asymptomatic hypocalcaemia without any skeletal anomaly was reported in the newborns (24).

Cost / cost effectiveness

No cost–effectiveness studies on bisphosphonates in osteogenesis imperfecta were identified in the application. Prices for intravenous zoledronic acid formulations per vial from different countries were reported in the application as: US$ 270 in Argentina, US$ 254 in Canada, US$ 35 in India and US$ 30 in Mexico. For the management of four 20 kg patients at a dose 0.05 mg/kg every 6 months, the annual cost per patient (assuming vial sharing) would be US$ 135 in Argentina, US$ 127 in Canada, US$ 18 in India and US$ 15 in Mexico.

WHO guidelines

WHO guidelines for the management of osteogenesis imperfecta are not currently available.

Availability

Zoledronic acid injection is available globally in both innovator and generic brands.

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