Alendronate sodium hydrate (oral jelly) for the treatment of osteoporosis: review of a novel, easy to swallow formulation

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Abstract: Osteoporosis is a skeletal disorder characterized by loss of bone mass, decreased bone strength, and an increased risk of bone fracture. The disease progresses with age, especially in postmenopausal women. Japan is one of the most rapidly aging societies worldwide. Japanese individuals over 65 years of age constituted 23.0% of the population in 2010 and 25.1% to 25.2% as of 2013. The estimated number of people with osteoporosis in Japan is currently 13 million. Bisphosphonates increase bone mineral density by inhibiting osteoclast-mediated bone resorption, thereby reducing the risk of fractures. Alendronate sodium hydrate (alendronate) is a bisphosphonate that potently inhibits bone resorption and is used to treat osteoporosis. Sufficient water is required to take an alendronate oral tablet; insufficient water could result in digestive system diseases, such as esophageal ulceration. Elderly patients with swallowing difficulty may choke on the tablet. Taking a tablet with oral jelly is a method to prevent digestive system disease and reduce the choking hazard. Once-weekly alendronate oral jelly was approved in 2012 by the Ministry of Health, Labour, and Welfare of Japan as the world’s first drug for osteoporosis in a jelly formulation. It consists of a jelly portion and an air portion. The jelly formulation is smoothly discharged by pushing the air portion. Therefore, elderly patients with physical disabilities are able to easily take all of the jelly formulation from the package. In this review, this new formulation of alendronate sodium hydrate (oral jelly) is introduced and discussed in terms of osteoporosis treatment. This new formulation provides an alternative so that patients may select a method of dosing tailored to their preferences. Management of osteoporosis involves assessing fracture risk and preventing fractures. Higher adherence to the treatment of patients with osteoporosis and prevention of osteoporotic fractures are issues to be resolved.

Keywords: air-extruded jelly formulation, alendronate sodium hydrate, bisphosphonate, elderly person, oral jelly, osteoporosis

Introduction
Osteoporosis is defined as a skeletal disorder characterized by loss of bone mass, decreased bone strength, and increased risk of bone fracture.¹ The disease progresses with age, especially in postmenopausal women.² Japan is one of the most rapidly aging societies worldwide. According to the National Institute of Population and Social Security Research (Tokyo, Japan), Japanese individuals over 65 years of age constitute 23.0% of the population in 2010 and 25.1% to 25.2% as of 2013, meaning that more than one in four people in Japan are elderly. According to population-based epidemiologic studies, the estimated number of people with osteoporosis in Japan is 13 million, among which 130,000 suffer from hip fractures every year; 20,000 of these individuals die and 60,000 experience functional decline. The prevalence rate of vertebral fractures in Japan is reportedly comparable with or higher than in Caucasian populations, and is
Formulations of oral drugs and packaging containers for elderly patients

In addition to osteoporosis, many elderly persons suffer from cardiovascular disease, diabetes mellitus, and joint disease. To treat their diseases, they often use multiple oral drugs. There are several formulations of oral drugs (Table 1). Ease of swallowing and handling are preferable for medications, particularly those for elderly patients.

Studies on the construction of new pharmaceutical preparations and new packaging containers that are optimal for administration to elderly people conducted by the Ministry of Health and Welfare of Japan in the 1980s reported that most powder, capsule, tablet, and liquid drug formulations and most packaging containers were suitable for general healthy adults, but not for elderly persons. Development of new formulations of medicines suitable for elderly individuals with difficulty in swallowing and mastication, dry mouth, and artificial teeth was desired. In 1996, the Ministry of Health and Welfare of Japan reported that jelly, pudding-like, biscuit-like, and wafer-like formulations were preferable for elderly patients. Biscuit-like and wafer-like formulations were developed as orally disintegrating tablets, which were advanced and popular drug formulations. The oral jelly formulation was developed as an original formulation in Japan. Oral jelly formulations have many advantages: ease of swallowing, the ability to take the medication without water, lower risk of accidental ingestion, and optimal masking of drug taste.

In addition to drug formulations, packaging containers optimal for elderly individuals were developed in Japan. There are several types of packaging containers for oral jelly: a single-serving type (Figure 1), a stick type (Figure 2), and an air-extruded type (Table 2). According to a survey among individuals aged 65 and over, the air-extruded type was better than the single-serving type and the stick type. Elderly persons tend to suffer from a decline in physical performance. It is difficult for the elderly persons to handle the single-serving type when it involved peeling off the container’s seal and

<table>
<thead>
<tr>
<th>Table 1 Oral drug formulations</th>
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<tr>
<td><strong>Advantage</strong></td>
</tr>
<tr>
<td>Powder</td>
</tr>
<tr>
<td>Capsule</td>
</tr>
<tr>
<td>Tablet</td>
</tr>
<tr>
<td>Liquid</td>
</tr>
<tr>
<td>Jelly</td>
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About 30% of patients in their 70 s and 40% in those in their 80 s. A study of the prevalence of vertebral fractures in Hong Kong, Thailand, Indonesia, and Japan revealed that the prevalence of vertebral fractures in both men and women was highest in Japan for the younger (65–74 years) and older (≥75 years) age groups (36.6% and 37.6% for men, 18.8% and 28.7% for women, respectively). Bisphosphonates are known to increase bone mineral density by inhibiting osteoclast-mediated bone resorption and thereby reduce the risk of fractures. Several formulations containing bisphosphonates have been applied to the management of osteoporosis. Alendronate sodium hydrate (alendronate) is a bisphosphonate that potently inhibits bone resorption and is used for the treatment of osteoporosis. Alendronate produces a sustained reduction in the levels of biochemical markers of bone remodeling, returning them to the premenopausal range. It also increases bone mineral density and decreases the risk of osteoporotic fracture in postmenopausal women. Long-term intervention studies have shown that continuous alendronate therapy is associated with a sustained therapeutic effect on bone density and remodeling.

However, bisphosphonates including alendronate, suppress bone remodeling and thus may prevent the repair of microdamage. Nine patients reportedly developed spontaneous nonspinal fractures after 1 to 8 years of alendronate therapy, and histomorphometric analysis of the bone biopsy samples revealed severe suppression of bone turnover. In Japan, a patient with insufficiency fractures of the pubis and ilium related to severe suppression of bone turnover after nearly 3 years of alendronate therapy was reported. Recent papers reported side effects of both atypical femoral fractures and osteonecrosis of the jaw after 7 years of oral alendronate therapy. Bisphosphonates also have adverse gastrointestinal effects, such as erosions and ulcers in the stomach and small intestine, which are mediated by mitochondrial superoxide production and lipid peroxidation.

Alendronate oral tablets were produced and are used for the treatment of osteoporosis. Water is required with an alendronate oral tablet to help facilitate absorption, and the drug cannot be taken with other foods or drinks. The act of remaining upright for 30 minutes decreases the risk of ulcer formation. Most patients with osteoporosis are elderly. Elderly persons with dysphagia or swallowing difficulty may choke on the tablet. Taking a tablet with oral jelly is a method to prevent digestive system disease and reduce the choking hazard. In this review, this new formulation of alendronate sodium hydrate (oral jelly) is introduced and discussed in the treatment of osteoporosis.

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taking the jelly formulation with a spoon. For the stick type, it was difficult to take all of the jelly formulation by squeezing the packaging container. An air-extruded jelly formulation was developed as a new formulation comprising the jelly formulation and clean air under increased pressure.\textsuperscript{22–25} The jelly formulation is smoothly discharged by pushing the air portion. Therefore, elderly patients with physical disabilities are able to easily take all of the jelly formulation from the package. The questionnaire survey indicated the applicability of the air-extruded jelly formulation in elderly patients.\textsuperscript{26} A majority of the patients (63.9%, 69 of 108 subjects) intended to switch their present drug formulation to the air-extruded jelly formulation. Especially among subjects who presently took a powder formulation or more than five kinds of medications daily, a high ratio intended to switch to the air-extruded jelly formulation.

**Alendronate sodium hydrate (oral jelly)**

Alendronate oral jelly 35 mg (Bonalon\textsuperscript{®} Oral Jelly 35 mg; Teijin Pharma Limited, Tokyo, Japan) was approved in 2012 by the Ministry of Health, Labour and Welfare of Japan as the world’s first drug for osteoporosis in jelly formulation. Alendronate oral jelly 35 mg, administered once a week, was launched in 2012 (Figure 3). Once-weekly alendronate oral jelly comprises a jelly portion and an air portion, which features the air-extruded jelly formulation and makes it easy to take the jelly formulation when pushed by the air. Thus, the active ingredient in the once-weekly alendronate oral tablet 35 mg, which has been proven both safe and effective as an osteoporosis treatment, is offered in a jelly formulation.

A dissolution test and bioequivalence study, in accordance with the Japanese Guideline on Bioequivalence Assessment for Development of Additional Formulations and the Japanese Guideline for Bioequivalence Studies of Generic Products, were carried out to evaluate the bioequivalence of alendronate oral jelly 35 mg to the alendronate oral tablet 35 mg.\textsuperscript{27} In the dissolution test, the dissolution profiles of both formulations satisfied the criteria for judgment of similarities set forth in the Guideline. The bioequivalence study was carried out with an open-label, randomized cross-over (two-sequence, two-period) study design and included 32 Japanese healthy adult male volunteers. When the pharmacokinetic parameters of alendronate oral jelly 35 mg and alendronate oral tablet 35 mg were calculated from the serum alendronic acid concentration, the area under the blood concentration time curve (AUC) showed a mean $\pm$ standard deviation of $21.70 \pm 10.20$ ng hour/mL and $21.33 \pm 13.96$ ng hour/mL, and maximum concentration ($C_{\text{max}}$) was $9.60 \pm 4.36$ ng/mL and $9.03 \pm 4.93$ ng/mL, respectively (Table 3). The serum half-life ($t_{1/2}$) was $1.54 \pm 0.48$ hours and $1.47 \pm 0.50$ hours, respectively. The mean logarithmic AUC and $C_{\text{max}}$ were log
(1.049) and log (1.050), respectively, each within the criteria range, log (0.90) to log (1.11), for judgment of bioequivalence with the similarities in dissolution profiles. These results indicate that alendronate oral jelly 35 mg is bioequivalent to alendronate oral tablet 35 mg and suggest no difference in clinical efficacy and safety.

**Table 2** Current oral jelly products in Japan

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Application</th>
<th>Packaging container</th>
</tr>
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<tbody>
<tr>
<td>Calcium polystyrene sulfur</td>
<td>Hyperkalemia</td>
<td>Single-serving</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>Hydrocephalus</td>
<td>Single-serving</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>Alzheimer’s dementia</td>
<td>Single-serving</td>
</tr>
<tr>
<td>Amlodipine besilate</td>
<td>Hypertension</td>
<td>Stick</td>
</tr>
<tr>
<td>Lactulose</td>
<td>Hyperammonemia</td>
<td>Stick</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>Viral infection</td>
<td>Air extruded</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Chronic arterial</td>
<td>Air extruded</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Osteoporosis</td>
<td>Air extruded</td>
</tr>
</tbody>
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Discussion

In European and American studies, alendronate at a dose of 5 to 20 mg/day has consistently been shown to increase bone mineral density at the spine, hip, and other skeletal sites and to reduce the risk of all types of fractures.6–12,28–32 The Fracture Intervention Trial (FIT) comprised two independent but parallel studies with common recruitment conducted at 11 institutions in the United States. The alendronate dosage was 5 mg/day for 2 years, and was then increased to 10 mg/day.8,10 In the Phase III study, alendronate dosages ranged from 5 to 20 mg/day.9 In The Fosamax international trial (FOSIT) and The Long-Term Care Facilities Study (LTCFS), the alendronate dosage was 10 mg/day.

Compared to Caucasians, Asians have a smaller body size33 and a lower dietary intake of calcium.34 Because of these racial differences, the recommended drug dose established for Caucasians may not be appropriate for Asians. A small-scale, single-blind study of postmenopausal Japanese women indicated that a dosage of 2.5 mg/day was as effective as a dosage of 10 mg/day in increasing lumbar bone mineral density with 36 weeks of treatment. However, bone turnover markers changed more markedly and rapidly in the 10 mg/day group, and the incidence of adverse effects was higher in the 10 mg/day group. These findings suggest that a 10 mg/day dosage may be an overdosage for Japanese patients.35 A dose-range finding study in Japan concluded that the optimal daily dose of alendronate is 5 mg in a Japanese population.36 The study showed that alendronate at a dosage of 5 mg/day was effective in increasing lumbar bone mineral density, and the incidence of adverse effects was no different compared with the placebo control group after 24 weeks of treatment for Japanese patients with postmenopausal osteoporosis. The study also showed that serum parathyroid hormone and serum 1,25-dihydroxyvitamin D increased only in the 5 mg/day dose group.

Studies to evaluate the effects of alendronate for the treatment of Japanese patients have been carried out. A double-masked multicenter comparative study of Japanese

**Table 3** Serum pharmacokinetic parameters of alendronate

<table>
<thead>
<tr>
<th></th>
<th>AUC (ng hour/mL)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{1/2} (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral jelly 35 mg (n = 32)</td>
<td>21.70 ± 10.20</td>
<td>9.60 ± 4.36</td>
<td>1.54 ± 0.48</td>
</tr>
<tr>
<td>Oral tablet 35 mg (n = 32)</td>
<td>21.33 ± 13.96</td>
<td>9.03 ± 4.93</td>
<td>1.47 ± 0.50</td>
</tr>
</tbody>
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Note: Values are mean ± standard deviation.

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; t_{1/2}, serum half-life.

Figure 3 Alendronate oral jelly (Bonalon® Oral Jelly 35 mg).
patients with osteoporosis indicated that alendronate treatment at a dosage of 5 mg/day for 48 weeks was more efficacious than alfalcaldiol for increasing bone mineral density without serious drug-related adverse events.37 A 2 year, double-blind comparative study of Japanese patients with osteoporosis indicated that alendronate at a dosage of 5 mg/day significantly lowered the incidence of one or more vertebral fractures to a greater extent than did alfalcaldiol after 6 months or more of treatment.38 A consecutive 3 year follow-up study of Japanese patients demonstrated that continuous alendronate therapy at 5 mg/day is associated with a sustained therapeutic effect on increasing vertebral bone mineral density and reducing the risk of new vertebral fractures.39 A prospective study to assess vertebral strength and mechanical parameters in Japanese women with postmenopausal osteoporosis indicated that vertebral strength significantly increased by 26.9% from baseline at 12 months of 5 mg/day alendronate,40 and by 31.8% at 18 months,41 demonstrating a sustained therapeutic effect.

Once-daily treatment with alendronate has been shown to substantially increase bone mineral density and bone strength and to reduce the incidence of osteoporotic fractures. Dosing convenience is a key element in the effective management of any chronic disease, and is particularly important in the long-term management of osteoporosis. Alendronate must be administered after fasting with water only, at least 30 minutes before the first food of the day, which offers an additional degree of complexity. Thus, it is desirable to reduce the frequency of alendronate dosing without compromising treatment efficacy. Animal data support the rationale that once-weekly dosing with alendronate at 70 mg (seven times the daily oral treatment dose for Caucasians) could provide similar efficacy to that of alendronate at a dosage of 10 mg/day because of its long duration of effect in bone.42-44 In addition, animal studies have suggested that the potential for esophageal irritation, observed with daily oral alendronate, might be substantially reduced with once-weekly dosing.45,46 A randomized, double-blind, multicenter study to evaluate the efficacy and safety of oral alendronate once- and twice-weekly dosing regimens compared with daily dosing in postmenopausal women with osteoporosis showed that both the once- and twice-weekly dosing regimens fully satisfied the equivalence criteria relative to daily dosing therapy.47,48 This study also showed that there were fewer serious upper gastrointestinal adverse experiences and a trend toward a lower incidence of esophageal events in the once-weekly dosing group than in the daily dosing group. The study concluded that once-weekly treatment with alendronate would provide patients with a more convenient, therapeutically equivalent alternative to daily dosing and might enhance compliance and long-term persistence with therapy.

A therapeutic equivalence study of once-weekly and once-daily alendronate was also carried out in Japan. The efficacy and safety of treatment with once-weekly oral alendronate 35 mg were compared with those of once-daily oral alendronate 5 mg in a 52-week, randomized, double-blind, multicenter study of Japanese patients with osteoporosis.49 The study concluded that the efficacy and safety of the alendronate 35 mg once-weekly regimen were therapeutically equivalent to those of the alendronate 5 mg once-daily regimen.

For a 12 month period in the United States, a randomized and double-blind study to compare the efficacy and tolerability of once-weekly oral alendronate 70 mg and the once-daily oral selective estrogen receptor modular raloxifene 60 mg was carried out for the treatment of postmenopausal osteoporosis.50 The study concluded that the once-weekly alendronate 70 mg regimen produced significantly greater increases in spine and hip bone mineral density and greater reductions in markers of bone turnover than the once-daily raloxifene 60 mg regimen with similar safety and tolerability profiles. Risedronate is a bisphosphonate that, like alendronate, binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. Once-weekly risedronate oral tablets at a dosage of 35 mg/week (5 mg/day) have been produced and used to treat osteoporosis.

A study comparing the once-weekly alendronate 70 mg regimen with the once-weekly risedronate 35 mg regimen during 24 months showed that the former yielded significantly greater bone mineral density gains and larger decreases in bone turnover marker levels than the latter, with no difference in gastrointestinal tolerability.51 The US Food and Drug Administration approved the once-monthly oral ibandronate sodium tablet as the first once-monthly oral tablet in 2005. Ibandronate sodium is a bisphosphonate that inhibits bone resorption and is commonly prescribed for the treatment and prevention of postmenopausal osteoporosis.52,53 Once-weekly oral bisphosphonates have been associated with higher adherence compared with the once-daily formulations, although overall adherence has remained suboptimal.54-56 A study performed to assess whether once-monthly bisphosphonates are associated with improvements in adherence showed no evidence of improved adherence with once-monthly dosing relative to once-weekly dosing, although adherence with either weekly or monthly dosing was significantly better than that with once-
daily dosing. These study results suggest that merely reducing the dosing frequency of oral bisphosphonates is not enough to improve adherence.

Alendronate oral jelly, which features the air-extruded jelly formulation, is easy for elderly patients to use and take; most of these patients have physical disabilities and swallowing difficulty. Therefore, this new formulation of osteoporosis treatment may meet individual needs and improve adherence. In addition, alendronate oral jelly with its advantages of ease of swallowing and lower risk of accidental ingestion may reduce the incidence of adverse effects such as esophageal irritation.

Some limitations are apparent regarding alendronate oral jelly. First, there are no published clinical data for its use in the treatment of osteoporosis. An in vivo study to evaluate the use of alendronate sodium gel in the treatment of bone resorptive lesions in periodontitis was carried out. Osseous defects associated with chronic adult periodontitis were filled with alendronate sodium gel, and flaps were then sutured to obtain primary closures of the interdental papilla in the alendronate gel site. In the control site, the defects were left unfilled. The osseous defect improvement rate in the alendronate gel site after 6 months was 42.85% and showed significant improvement compared with that of the control site of (7.43%). In addition, a 6 month, randomized, controlled clinical trial showed that the local delivery of 1% alendronate gel into periodontal pockets significantly improved bone filling compared with a placebo gel. Second, alendronate oral jelly is approved and used only in Japan. Clinical data in Japan will lead to approval in other countries. Third, once-weekly dosing of alendronate oral jelly is the only dosing regimen. Other options, such as a once-monthly dosing regimen, will create a variety of osteoporosis treatments to meet individual needs. Intravenous infusion of alendronate for the treatment of osteoporosis is one of these therapeutic options. This preparation may avoid the topical effects of oral alendronate on the gastric mucosa and may provide a useful alternative to oral dosing. A 52-week, multicenter, randomized, double-masked, active-controlled, parallel-group, non-inferiority study of different preparations of alendronate for the treatment of osteoporosis involves assessing fracture risk and preventing fractures. Higher adherence of treatment of patients with osteoporosis and prevention of fractures associated with osteoporosis remain issues to be resolved.

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Disclosure
The author reports no conflicts of interest in this work.

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