

# Disintegration and Esophageal Irritation Profiles of Alendronate Formulations: Implications for Clinical Safety and Efficacy

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## ABSTRACT

**Background:** Fosamax (alendronate sodium, Merck & Co., Inc., Whitehouse Station, NJ, USA) is an effective oral bisphosphonate widely used to treat and prevent osteoporosis, with a safety and tolerability profile similar to placebo in clinical trials. It has been evaluated in clinical trials with over 20,000 participants and up to 10 years duration. Oral bisphosphonates have been associated with esophagitis, which involves events that occur prior to absorption and depends on factors such as the frequency of administration, dose, and formulation. Data on non-Fosamax alendronate (NFA) preparations, which contain a form of alendronate with differing

excipients, are typically derived from small, single-dose, bioavailability studies. While these studies provide information on systemic effects, they do not address the risk of local esophageal irritation and may, therefore, inadequately characterize safety profiles.

**Objective:** To compare the esophageal irritation potential of NFA preparations to that of the innovator medication, Fosamax.

**Methods:** Two preclinical models of irritation were used. In the first, 24 rabbits were randomized to a single, subcutaneous injection of saline, 10.6 mg of Fosamax in saline, or 10.6 mg NFA in saline. Blinded measurements of skin thickness (a measure of inflammation), wet weight, and histopathology of injection site tissues were performed. In the

second study, 16 dogs were anesthetized and a placebo tablet, a 10-mg Fosamax tablet, or a 10-mg NFA tablet was placed by endoscopy in the caudal third of the esophagus for 1 hour, followed by a saline rinse, daily for 5 days. After the final dose, the dogs were sacrificed and esophageal morphology was examined.

**Results:** In the rabbit injection study, the NFA suspension elicited a significantly greater irritant response than an equivalent suspension of Fosamax. The mean wet weight increase at injection site tissues was 70% greater ( $P < 0.01$ ) for NFA than Fosamax. Fosamax treatment induced smaller, predominantly foreign-body granuloma type lesions, while NFA induced larger, encapsulated cystic lesions containing the injected material, consistent with a post-inflammatory process. In the esophagus study, all 4 dogs (100%) treated with NFA for 5 days exhibited marked ulcerative esophagitis, whereas only 1 of the 5 dogs treated with Fosamax (20%) had marked ulceration; the remaining 4 dogs had more moderate esophageal changes than those observed in dogs treated with NFA.

**Conclusions:** Generic drugs are expected to have similar efficacy and safety to innovator drugs; however, the greater irritant responses of NFA in rabbits and dogs suggest that important differences may exist between the effects of Fosamax and NFA preparations in the clinical setting. These findings, along with other data demonstrating differences in the disintegration/dissolution profiles of NFA preparations relative to Fosamax, suggest that bioavailability studies may not be adequate for meaningful assessment of the safety and efficacy of NFA or other bisphosphonate preparations.

## INTRODUCTION

Fosamax (alendronate sodium, Merck &

Co., Inc., Whitehouse Station, NJ, USA) is a nitrogen-containing oral bisphosphonate (N-BP) that exhibits a potent and selective inhibitory effect on osteoclast-mediated bone resorption. It has been evaluated in clinical trials with more than 20,000 participants and up to 10 years' duration and is approved worldwide for the treatment of postmenopausal osteoporosis.<sup>1-3</sup> Fosamax is also an established therapy for the prevention of osteoporosis.<sup>4</sup> It is approved in all guidelines for the treatment of osteoporosis in postmenopausal women, in men, and in patients with glucocorticoid-induced osteoporosis.<sup>5</sup> Treatment with Fosamax has been shown to reduce bone turnover and increase bone density, producing decreases in the incidence of osteoporotic fractures, including those at the spine and hip, of approximately 50%.<sup>6,7</sup> Fosamax was initially available as a 10-mg daily tablet and subsequently developed as a 70-mg once-weekly formulation. The daily and weekly doses were determined to be therapeutically equivalent in a large randomized controlled clinical trial.<sup>8,9</sup>

Appropriate dosing is important to ensure both efficacy and safety for bisphosphonates. The product should be taken with a full glass of water and the patient should remain upright at least 30 minutes before the first food or beverage of the day.<sup>10</sup> Cases of esophagitis have been reported in clinical use, primarily associated with poor adherence to the dosing instructions.<sup>11-13</sup> This is a general characteristic of oral bisphosphonates, as described in the product labels for each bisphosphonate on the market. The safety and tolerability profile of Fosamax is consistently similar to placebo in each of several large clinical trials<sup>1-4,6,14</sup> and to other approved N-BPs evaluated in head-to-head clinical trials in which the only gastrointestinal exclusion criterion was conditions associated with delayed esophageal emptying,<sup>15</sup>

suggesting it is generally safe when taken as directed. By contrast, non-Fosamax alendronate (NFA) preparations (marketed in some countries) have not been evaluated extensively, and one study reported substantial differences in the disintegration/dissolution profiles of these preparations relative to innovator Fosamax.<sup>16</sup> Those findings suggest that important differences may exist between NFA preparations and Fosamax with regard to bioavailability and pharmacokinetics, and that the products may not necessarily provide the expected similar safety and efficacy for reasons described previously.<sup>16,17</sup>

The purpose of the present study was to extend the earlier studies by comparing the upper gastrointestinal safety profile of NFA tablets to that of innovator Fosamax in 2 animal models of local irritation, and to consider the clinical implications of these data together with previous findings.

## **METHODS**

Fosamax and NFA were compared in 2 studies: a rabbit skin model of local irritation, and a dog esophageal irritation model.

### **Rabbit Skin Model Of Local Irritation**

Skin thickening is a measure of the irritant/inflammatory response that can be followed over time in living animals. The model described here has been used previously as a surrogate model of esophageal irritation.<sup>18</sup> By measuring skin thickness, the dynamics of local irritation can be monitored over prolonged periods without requiring euthanasia of large numbers of animals to obtain data at multiple time points. At study termination, the local irritant effects can be verified via postnecropsy analyses of the affected tissue. This includes measurement of the wet weights of the inflamed tissue and histopathology analyses.

**Animals, Dosing, and Skin-Thickness Measurements.** Twenty-four approximately 3.5-kg New Zealand White rabbits (Charles River Breeding Laboratories, Saint Constant, Quebec, Canada) were randomized, 8 per group, to one of 3 treatment groups (vehicle, Fosamax, or NFA), balanced by weight. Animals were given ad libitum access to water and standard rabbit chow. Animals were shaved in the mid-scapular region and a 3-cm circle drawn to define the injection site. Baseline skin thickness measurements were taken in the morning using a digital caliper to lightly pinch a fold of skin at the prepared injection site. In the afternoon, injection sites were disinfected with 70% isopropanol and topical anesthetic was applied.

For dosing suspensions, 22.5 mL of sterile isotonic saline were stirred with 15 tablets of either Fosamax or NFA (alendronate sodium; NOVO-Alendronate, Novopharm, Toronto, Canada) for more than 30 minutes prior to injecting to allow complete dissolution of alendronate. The calculated amounts of alendronate in 1.6 mL of dosing suspensions were 10.61 mg for Fosamax and 10.68 mg for NFA, suggesting 99.3% accuracy in administration. For each dosing, 1.6 mL of vehicle, Fosamax, or NFA suspension was withdrawn from an actively stirring preparation into a sterile, disposable 3-cc syringe using an attached sterile 18-gauge needle, and this was immediately administered at the center of the marked site. Blinded skin thickness measurements were performed on Mondays, Wednesdays, and Fridays, beginning on the second day after dosing and continuing for 40 days after the baseline measurement.

At study termination all animals were euthanized following administration of a sedative (Ketamine/Xylazine, 50/10 mg/kg IM) using intravenous sodi-

um pentobarbital (120 mg/kg). Injection sites were dissected out within approximately 5 minutes of euthanasia, and specimens were immediately immersed in 10% neutral-buffered formalin for fixation. Data from one animal in the Fosamax group that developed a bacterial infection at the injection site were excluded from all analyses.

**Wet Weights and Histology.** After 10 days of fixation, injection site tissues were rinsed with, and then transferred into, 70% ethanol. Specimens were then trimmed to include only the marked sites (vehicle) and/or the thickened regions extending beyond the marked site, and weighed in a blinded manner.

For histology, one transverse cut was made through the maximally thickened (or center) subregion of each injection site. Halved specimens were paraffin-embedded, and 5- $\mu$ m sections were then prepared for microscopy by standard methods. One section from each sample was stained with hematoxylin-eosin and a second was stained with Massons Trichrome to permit characterization of fibrotic tissues. Stained sections were blindly evaluated by a veterinary pathologist (S.L.H.) for necrosis, granuloma formation, cyst formation, mineralization, intralesional vacuolation, macrophage infiltration, and presence of multinucleated giant cells, polymorphonuclear leukocytes (heterophils), lymphocytes, plasma cells, and foreign material.

**Statistical Analysis.** Repeated measures analysis of variance (ANOVA) was performed on skin thickness data using SAS software version 8.0.1. (SAS Corporation, Cary, NC, USA). Other statistical analyses of skin thickness and wet weight were by Fisher's Protected Least Significant Difference (PLSD) and ANOVA using StatView for

Windows software, version 5.0.1. (SAS Corporation, Cary NC, USA).

### **Dog Esophageal Irritation Study**

The dog model used in the present study has been described previously, having been developed to examine the mechanism of bisphosphonate-induced esophageal irritation as a function of pH and frequency of exposure.<sup>19</sup> In brief, when dogs are anesthetized, the esophageal sphincter closes, enabling the placement of tablets or solutions in the caudal esophagus for fixed periods of time to assess the effect on the esophagus. Animals were sacrificed after the final exposure and the esophagus was evaluated for gross and histologic changes.

Two similarly designed, comparative experiments were conducted: in the first, dogs were randomized to receive either 10-mg NFA tablets (n = 4; alendronate sodium, Teva Pharmaceutical Industries Ltd., Petah-Tikva, Israel) or placebo Fosamax tablets (n = 3). In the second study, dogs were randomized to either placebo Fosamax tablets (n = 4) or 10-mg Fosamax tablets (n = 5).

Female beagle dogs (Marshall Farms, USA, Inc., North Rose, New York, USA), aged 51 to 54 weeks and weighing 5.7 kg to 7.1 kg, were fasted overnight prior to dosing and received 350 g standard canine diet for approximately 2 hours each day following dosing and recovery. Dogs were assigned to treatment groups based on a weight-balanced random allocation scheme and were treated for 1 hour once daily for 5 days.

**Medication Administration.** General anesthesia was induced with thiopental sodium (2.5%) at a dose of approximately 15 mg/kg to 25 mg/kg, an endotracheal tube was inserted, and anesthesia was maintained throughout

the procedure using isoflurane gas. An Olympus gastrointestinal endoscope was used to place the placebo or NFA product tablet in a similar location during each daily administration; the endoscope (shielded to prevent the tablet from becoming moist) was inserted to a distance of 25 cm to 30 cm down the esophagus of all dogs. The forceps were advanced to a distance of 4.0 cm from the endoscope tip, and the tablet was dropped onto the esophageal mucosa. If necessary, air was suctioned from the esophagus to ensure optimal contact of the tablet with the esophageal mucosa. The endoscope was then removed.

After 1 hour, the endoscope was again advanced into the esophagus until the remnants of the tablet were visualized, and 5 mL of sterile water were flushed from the tubing to dislodge the tablet remnants from their original location in the esophagus. If necessary, air was suctioned from the esophagus and the scope was then removed. Isoflurane was discontinued, and the animals were allowed to recover from anesthesia.

The animals were examined daily for mortality and drug-related clinical signs. Body weight measurements were performed twice during a 2-week acclimation period and again on the day of randomization. During the treatment period, animals were weighed on day 3 and day 5. Food consumption was measured daily during the 5-day pretreatment period and from day 1 to day 4.

***Necropsy and Histomorphology.*** Three samples (one from the cranial third, one from the middle third, and one from the caudal third) of the esophagus, which included any grossly observed changes, were fixed in 10% neutral buffered formalin. Histology processing and histomorphological evaluation of tissue samples were conducted by Merck Research Laboratories (West Point, PA, USA). Paraffin-embedded and hema-

toxylin- and eosin-stained sections of the esophagus from all sampled regions were prepared by routine procedures and examined using light microscopy.

## **RESULTS**

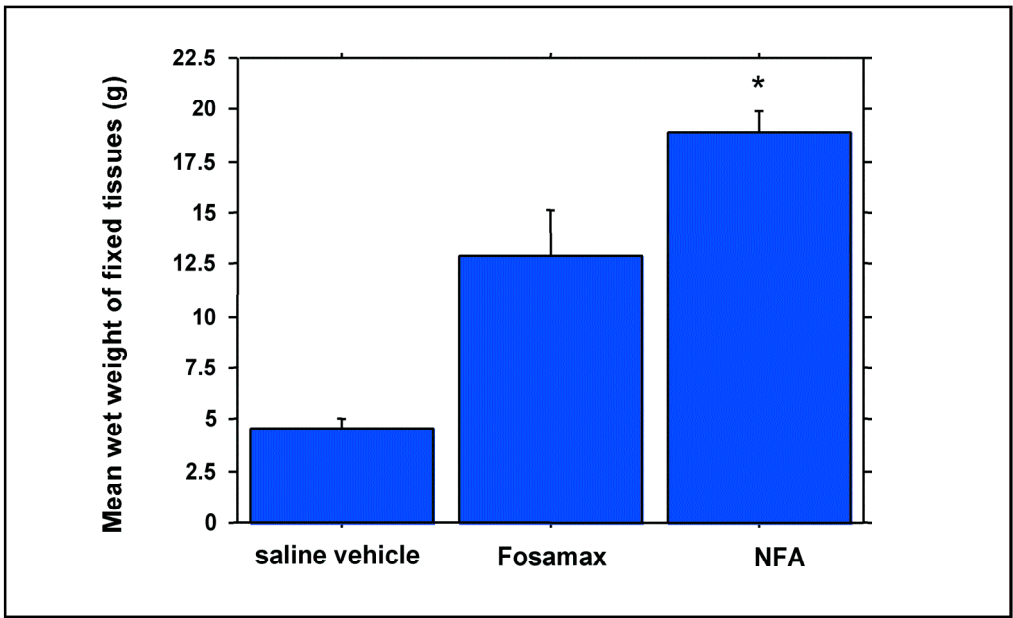
### **Rabbit Skin Model of Esophageal Irritation**

#### ***Skin Thickness and Wet Weight***

***Measurements.*** Mean skin thickness was numerically greater in the NFA group than in the Fosamax group for all time points after baseline. Statistically significant differences ( $P < 0.05$ ) between mean skin thicknesses in the Fosamax versus the NFA groups were observed at days 5, 8, 10, 22, and 36. Repeated measures ANOVA revealed a statistically significant overall difference between the two groups ( $P = 0.034$ ). In the repeated measures analyses, comparison of saline vehicle versus NFA yielded a  $P$ -value of  $< 0.0001$  and vehicle versus Fosamax yielded a  $P$ -value of 0.017.

At the end of the study, the increase in mean wet weight of injection site skin specimens dissected from animals at sacrifice was 70% greater ( $P < 0.01$ ) for NFA-treated animals relative to those that had received Fosamax (Figure 1).

***Histopathology.*** Analysis of injection site tissue specimens indicated differences in the character of tissue-level irritant responses elicited by suspensions of Fosamax versus those of the NFA formulation. Whereas Fosamax treatment was associated with a predominantly foreign-body granuloma type response, NFA treatment produced a larger cystic nodule (Figure 2). In the Fosamax treatment group, nodules were smaller and were characterized by a thick rim of multinucleated giant cells mixed with activated macrophages and a central accumulation of foreign material (tablet suspension material). In the NFA group, the lesions were larger and devoid of significant inflammatory cell infiltrate,



**Figure 1.** Mean wet weight of formalin-fixed rabbit skin injection site tissues. \* $P < 0.01$  versus Fosamax.

which may be indicative of a postinflammatory process, and tablet suspension material was encapsulated by fibrous tissue. Both treatments elicited adipocyte necrosis in basal and lateral regions of nodules. Control animals exhibited no lesion formation.

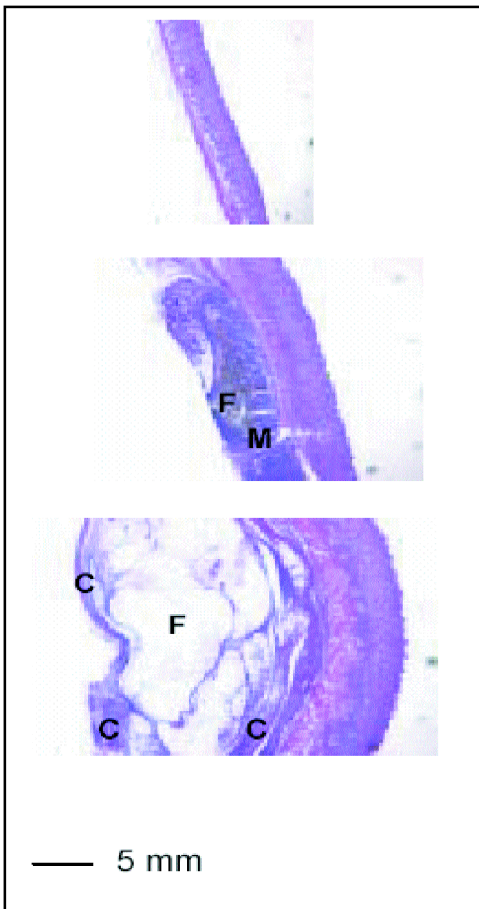
The Fosamax diagnosis was subcutis, foreign body granuloma, multifocal to coalescing, chronic, moderate to severe, with centralized foreign material and adjacent fat necrosis. The NFA diagnosis was subcutis, fibrous cyst, focal, chronic, moderate to severe, with centralized foreign material and adjacent fat necrosis.

### Dog Esophageal Irritation Study

There were no treatment-related changes in body weight, food consumption, or behavior, and no dogs died. There was no treatment-related gross or histologic evidence of tissue damage in the cranial or mid-esophagus in any sample, confirming that damage was not caused by the procedure.

At necropsy, all 4 dogs exposed daily for 5 days to NFA tablets showed

multiple, raised, and discolored foci in the caudal esophageal mucosa. These gross changes were present in the region where the tablets had been placed and corresponded histomorphologically to areas of marked ulcerative esophagitis in all four dogs (Table 1). The histomorphologic changes in dogs exposed to NFA were characterized by necrosis of stratified squamous epithelium lining the lumen of the esophagus and partial to complete loss of mucosal lining (ulceration) (Figure 3). The inflammatory response associated with the ulceration consisted of large numbers of neutrophils within the necrotic and disrupted epithelial lining and within the underlying submucosa. Marked submucosal edema was also present. Early reepithelialization, consistent with an early reparative process, was observed near the margins of the esophageal injury. In contrast, most of the changes observed in dogs exposed to Fosamax 10 mg daily for 5 days were more moderate than those observed in dogs exposed to 5 days of 10-mg NFA (Figure 3); only 1 of

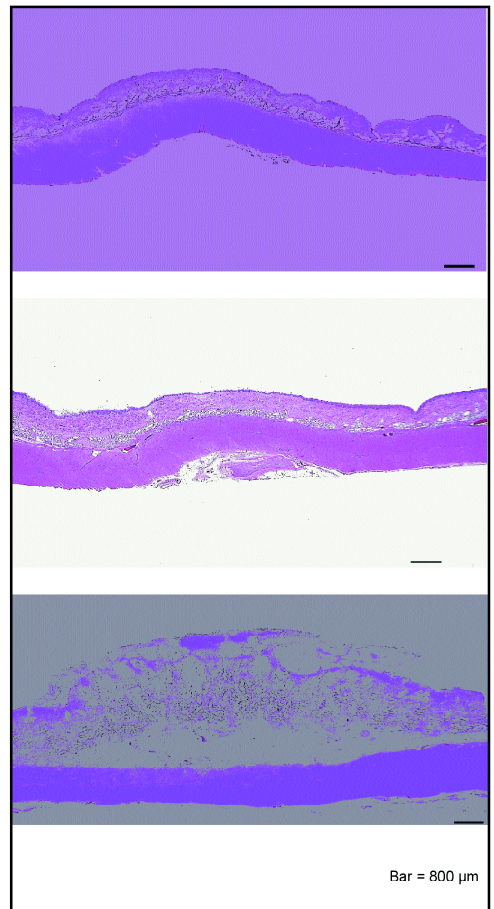


**Figure 2.** Representative photomicrographs of rabbit skin injection sites 40 days after a single subcutaneous dose of vehicle (top panel), Fosamax (middle panel), or non-Fosamax alendronate (NFA) (bottom panel). F indicates foreign material; M, macrophage and giant cell infiltrate; C, margins of fibrous cyst.

the 5 dogs treated with 10 mg Fosamax for 5 days had marked caudal esophagus changes (Table 1).

## DISCUSSION

Esophagitis is a potentially serious and important local adverse event associated with the use of bisphosphonates. While the incidence of cases has been reduced with proper dosing instructions, cases are still reported and the risk remains, especially in real-world use. One would expect NFA and Fosamax to produce similar degrees of irritation in the pre-



**Figure 3.** Photomicrographs of the caudal dog esophagus at sites exposed to placebo (top panel), Fosamax (middle panel), or non-Fosamax alendronate (NFA) (bottom panel) for 1 hour per day for 5 days; these images are representative of normal, less severe, and more severe esophageal tissue changes, respectively.

clinical models of esophageal irritation used here, because both formulations contained similar amounts of alendronate. However, the present findings demonstrate a greater irritant response to NFA compared with Fosamax in rabbit and dog models used in this study. Subcutaneous injection of rabbits with NFA suspension elicited significantly greater irritation than was produced by an equivalent dose of Fosamax, as measured by skin thickness and wet weight. Similarly, esophageal exposure to daily 10-mg NFA tablets for 5 days caused

**Table 1.** Caudal Esophagus Histologic Findings Following 5 Days of Repeated Esophageal Exposure\*

Histologic findings	Placebo (n = 3)	Non- Fosamax Alendronate (n = 4)	Placebo (n = 4)	Fosamax (n = 5)
No irritation	3	0	4	0
Erosive esophagitis				
Slight	0	0	0	1
Moderate	0	0	0	2
Ulcerative esophagitis				
Moderate	0	0	0	1
Marked	0	4	0	1

\*n values represent number of dogs.

greater irritation in dogs than that produced by an equivalent dose and duration of Fosamax tablets. These results provide evidence for potential increased esophageal irritation with NFA in clinical practice, and resulting increase in number of events or severity (eg, more perforations).

**Localized Skin Responses in Rabbits**

Skin irritation elicited by N-BPs in rabbits has been modeled as a surrogate for gastrointestinal tract irritation following oral dosing in humans, since these tissues are both known to be affected by local exposure to bisphosphonates.<sup>20</sup> Although differences exist in the cellular processes underlying esophageal versus subcutaneous inflammatory responses, irritant effects of subcutaneous exposure to N-BPs may index analogous reactions in the esophageal lining. Recent studies suggest that skin and upper gastrointestinal tract irritation produced by N-BPs is mechanistically linked to the bone-sparing effects of these compounds, via inhibition of the same cholesterol synthesis metabolic pathway.<sup>21</sup> Thus, one would expect similar degrees of tissue irritation using equivalent amounts of the active compound, alen-

dronate. However, the magnitude of skin thickening and wet tissue weight increase elicited by NFA was significantly greater than that produced by Fosamax. The larger differences in wet weights compared to skin thickness suggest that the measurements of skin thickness underestimated the difference in irritation response between the 2 groups. Furthermore, histopathology analysis revealed qualitative differences in tissue-level inflammatory responses between NFA and Fosamax. These results suggest that aspects of tablet formulation other than those related to the active component (alendronate) may increase the tissue irritation potential of NFA tablets. While not definitive, the greater irritant effects at subcutaneous injection sites in rabbits suggest that NFA may have greater potential to cause esophageal irritation in humans, compared to Fosamax.

**Esophageal Irritation in Dogs**

The dog model used in the present study was developed to assess the mechanism of esophageal irritation with alendronate.<sup>19</sup> Prior studies using this model have demonstrated that repeated, daily exposure to an alendronate solution at



pH 2.0 (similar to the pH of gastric juice) resulted in esophagitis, but esophagitis was not observed with similar dosing at higher pH (3 and 5).<sup>19</sup>

The present findings demonstrated marked ulcerative esophagitis in all dogs exposed to NFA, whereas more moderate changes were observed in most dogs exposed to Fosamax. As with the results observed in the rabbit model of esophageal irritation, these findings raise concern about the potential for esophagitis with clinical use of NFA preparations. Moreover, this potential effect would likely be more severe if reflux of acidic gastric contents into the caudal esophagus were to occur during dosing in the clinical setting.

### **Clinical Implications**

In addition to the present findings demonstrating that NFA is more irritating in preclinical models of esophageal irritation, other factors may influence the clinical efficacy and safety profiles and should be considered.

### ***Variability in Disintegration Profiles.***

Prior research has shown notable differences in the physical properties of some NFA preparations compared with Fosamax that may impact both safety and efficacy.<sup>16</sup> Some NFA tablets disintegrated 2- to 10-fold faster than Fosamax, whereas other NFA tablets disintegrated at least 5-fold slower (Figure 4).<sup>16</sup> Further evaluation of one slow-disintegrating NFA product demonstrated that the release of alendronate into solution lagged behind that from Fosamax.<sup>16</sup>

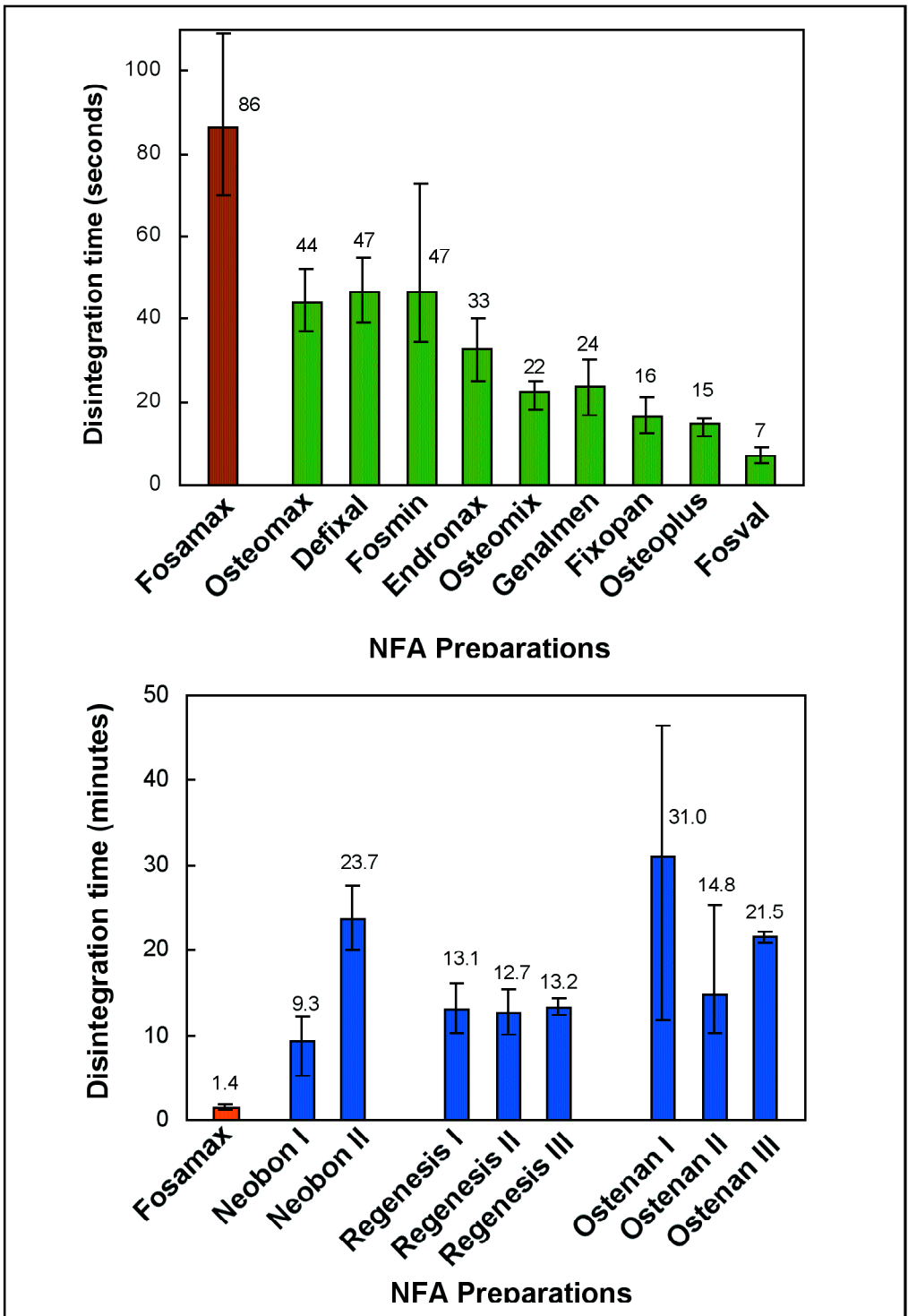
Delayed disintegration could increase the chances of irritation if the tablet or fragments of the tablet become stuck or reflux into the esophagus. For instance, a delayed-release 30-mg risedronate tablet for the treatment of Paget's disease was abandoned in favor of an immediate-release formulation due to reports of esophagitis.<sup>22</sup> On the

other hand, if tablets disintegrate too quickly, particles may be retained in the mouth or esophagus, leading to irritation. An even higher incidence of pill esophagitis would be expected in patients with motility disorders that delay esophageal transit or patients with esophageal reflux disease who do not adhere to dosing instructions.

Furthermore, a difference in disintegration times for NFA preparations relative to Fosamax could impair absorption and reduce efficacy.<sup>16</sup> Disintegration too soon could leave alendronate in the mouth or esophagus where it may not be absorbed. Conversely, slow disintegration would increase the likelihood that the tablet would come into contact with ingested food or liquids before adequate absorption can occur.

***Other Factors.*** Other factors (including tablet size, density, shape and coating, granulation and crystallization characteristics, and type of excipients) may influence the esophageal safety and bioavailability of NFA preparations independent of their effects on disintegration time. Some of these formulation factors may be responsible for the differences in irritation observed in the current study. There are notable differences in excipients between Fosamax and various NFA preparations, which may alter disintegration profiles and other aspects including safety and efficacy. The tendency of products to adhere to the esophageal mucosa can be modified by shape and formulation, including coating material.<sup>23</sup> For instance, gel capsules have longer esophageal transit times relative to tablets due to a greater tendency for adherence.<sup>23-25</sup> Severe upper gastrointestinal adverse events were reported in a previous trial of pamidronate gel capsules;<sup>26</sup> thus, recent bisphosphonate development programs have avoided the use of gel capsules.

In addition to formulation, manufac-



**Figure 4.** Disintegration times in water at 37°C of different preparations of non- Fosamax alendronate (NFA) that disintegrated faster (top panel) or slower (bottom panel) than Fosamax. Error bars represent the range of individual values measured.

turing processes can affect granulation and crystallization characteristics;<sup>27</sup> any of these factors may influence the extent of drug absorption and thus might influence the acceptable interval between administration and subsequent food intake. This is very important with bisphosphonates since absorption depends on pH level and local salts in the gut and is almost completely abolished in the presence of food.<sup>28</sup> The manufacturer of Fosamax does not sell alendronate for further processing or distribution by other entities and, to our knowledge, there is no publicly available information regarding the manufacturing source(s), processes, or amounts of alendronate in most NFA preparations.<sup>16,17</sup> Indeed, it was previously reported that at least one NFA preparation did not contain the amount of alendronate stated on the product label.<sup>29</sup>

### **Bioequivalence: What Constitutes Proof?**

In some countries, NFA preparations have sought, and in some instances obtained, approval for marketing based exclusively on data from small, single-dose bioavailability studies relative to Fosamax. However, such studies have major limitations and may not accurately indicate the clinical safety and efficacy of NFA preparations. For example, some have measured bioavailability using long fasting times of up to 5 hours after dosing with NFA. Since food and beverages strongly interfere with absorption of alendronate,<sup>28</sup> long fasting times could increase the amount of alendronate absorbed, and comparisons to previous studies of Fosamax that used shorter fasting times could be misleading. Also, unlike many other drugs, the pharmacological action and relevant exposure level of bisphosphonates is not determined by the levels circulating in the blood, but instead by the cumulative amount deposited on the bone surface,

which will increase with repeated dosing and cannot be directly measured in humans. In addition, bioavailability of oral bisphosphonates is highly variable, and small studies could easily fail to detect clinically important differences in bioavailability of 20% or more, due to Type II statistical errors. Moreover, the potential for esophagitis with oral bisphosphonates involves processes that occur *prior* to absorption and is related to the frequency of dosing and other factors. Thus, due to these unique characteristics, even small differences in tablet disintegration rates, types of excipients, and formulation characteristics between a test and reference bisphosphonate might result in important differences in safety and efficacy that would not be detected in small, single-dose bioavailability studies.

An example of the potential risks of approval and use of such drugs in the absence of direct safety information was observed in 2001, when some patients were switched from Fosamax to an NFA preparation (which had been approved on the claim of similar bioavailability) and many began to experience significant gastrointestinal adverse experiences, including 1 case of esophageal rupture.

Thus, given the unusual characteristics of bisphosphonates and the influence of seemingly minor differences in formulation, it appears that simple bioavailability studies may not be adequate for predicting the clinical efficacy and safety profiles. Given the problems with using bioavailability data alone, large clinical trials of each new formulation may be required to assess its safety before NFA products are prescribed.

### **CONCLUSION**

In the present study, NFA was more irritating than Fosamax in two preclinical models of esophageal irritation. These data, together with previous findings

demonstrating differences in the disintegration/dissolution profiles of NFA preparations relative to Fosamax, suggest that important differences may exist between Fosamax and NFA preparations regarding clinical safety and efficacy. Additional studies, including large clinical trials, may be necessary to adequately evaluate the clinical efficacy and safety of NFA products.

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