

BRIEF REPORT

Disintegration/dissolution profiles of copies of Fosamax (alendronate)

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SUMMARY

Objective: Poor quality has been reported for some generics and other copies of original products. We performed a pilot study to compare the disintegration/dissolution profiles of FOSAMAX (alendronate) 70 mg tablets with those of copies of FOSAMAX that were manufactured outside the United States.

Research design and methods: We used the standard United States Pharmacopeia (USP) disintegration method to evaluate FOSAMAX 70 mg tablets and 13 copies. At least 12 ($n = 12$) dosage units were tested for each product (except Fosmin, $n = 10$). The dissolution profiles of FOSAMAX and one representative copy were also compared.

Results: Nine copies (Osteomax, Defixal, Fosmin, Endronax, Osteomix, Genalmen, Fixopan, Osteoplus, and Fosval) disintegrated two- to ten-fold faster than FOSAMAX. Three other copies (Neobon, Regenesis, and Ostenan) disintegrated at least five-fold slower than FOSAMAX. Neobon is a softgel capsule, so special consideration was

given to this different dosage form. One copy (Arendal) did not fall into either category but exhibited potentially large inter- and intra-lot variability. Dissolution of alendronate from Regenesis lagged behind that from FOSAMAX.

Conclusion: Slower disintegration may reduce efficacy because bisphosphonates must be taken in the fasting state and contact with food or even certain beverages severely reduces bioavailability. Faster disintegration (or the use of gel-caps or other alterations to the drug formulation) could increase the risk of esophagitis, an adverse event associated with prolonged contact of the esophagus with bisphosphonates. These disintegration and dissolution results suggest that important differences may exist between FOSAMAX and its copies with regard to bioavailability, pharmacokinetics, and clinical efficacy and safety profiles. Additional testing is warranted to evaluate the pharmacokinetics and clinical safety of these copies.

Introduction

The World Health Organization (WHO) has reported numerous examples of inferior quality for copies of original pharmaceutical products¹. In some cases, the substandard drugs contained incorrect ingredients or lacked the stated ingredient altogether. Moreover, even when the stated ingredient was present, in some cases it did not dissolve adequately or the amount was incorrect². For example, differences in formulation and manufacturing can lead to differences in bioavailability from one finished product to another¹. In particular, '...for oral generic forms, a bio-equivalence study against the innovator product will be required except when a single *in vitro* dissolution comparison is proved to be sufficient'¹.

FOSAMAX (alendronate sodium)^a – an oral bisphosphonate – is a potent and selective inhibitor of osteoclast-mediated bone resorption that has been evaluated in clinical trials of up to 10 years' duration involving more than 19 000 patients, including men with osteoporosis and postmenopausal women³⁻⁸. Treatment with FOSAMAX was associated with reductions in bone turnover and increases in bone density, resulting in decreases of approximately 50% in the incidence of osteoporotic fractures of all types, including those at the spine and hip^{7,9,10}. FOSAMAX was originally available as a 10 mg daily treatment, and later developed as a once-weekly 70 mg formulation; a large clinical trial demonstrated that the two dose regimens are therapeutically equivalent³.

Despite existing unexpired patents on FOSAMAX, some Latin American and Asia-Pacific countries allow copies of FOSAMAX to be marketed. The definition of generic drug is a copy of an original medicinal drug '...whereby production and marketing are made possible by the expiry of the patent covering the innovator product'¹. Since FOSAMAX is still protected by patent and the bioequivalence of other products is currently unknown, we refer to the other preparations as copies instead of generics in the current report.

The bioavailability and absorption of bisphosphonates may depend on manufacturing, formulation, and hence on tablet performance, to a large degree. The presence of food or beverages other than water substantially reduces the bioavailability of bisphosphonates relative to water; absorption is impaired even when taken 2 h after breakfast. Due to their limited bioavailability, most oral bisphosphonates, including FOSAMAX, should be taken on rising in the morning, before the first food or beverage of the day¹¹. Furthermore, food and beverages other than water should be withheld until at least 30 min after dosing to ensure that the drug is delivered to the stomach and absorbed without interference.

These characteristics of bisphosphonates suggest that seemingly minor deviations in dosing regimen, disintegration, and dissolution may have important effects on bioavailability and safety (see Discussion).

Oral bisphosphonates (alendronate, risedronate, pamidronate, etc.) have the potential to irritate the upper gastrointestinal tract¹². Therefore, safety assessments have focused on the upper gastrointestinal tract. Case reports of esophagitis with the use of bisphosphonates have been described¹²⁻¹⁴. Nevertheless, FOSAMAX has exhibited safety and tolerability profiles similar to placebo in large clinical trials^{3-10,15,16}, suggesting that proper administration can help minimize the risk of upper GI problems¹². Like most oral bisphosphonates, FOSAMAX should be taken with a full (6- to 8-ounce) glass of water¹¹. Drinking sufficient water helps to ensure that the tablet clears the esophagus rapidly. Patients are instructed not to lie down for at least 30 min after dosing to limit the risk of refluxing the bisphosphonate up the esophagus¹¹.

Given these considerations, it is reasonable to hypothesize that the time necessary for full disintegration of FOSAMAX tablets may have important implications for alendronate bioavailability, pharmacokinetic properties, efficacy and safety. The purpose of this pilot *in vitro* study was to compare the disintegration time of several copies commercially available on the Latin American markets to that of original FOSAMAX 70 mg. The dissolution profile of one copy (Regenesisc^b) was also compared to FOSAMAX.

Materials and methods

Copies Investigated

Table 1 lists the names of 13 copies marketed in eight Latin American countries as tablets with or without a film coat, with the exception of Neobonc^c which is a softgel capsule. Qualitative excipient information from product package inserts indicated that Endronax^d, Regenesisc, and Arendal^e contain lactose and microcrystalline cellulose (as does FOSAMAX), and also contain either croscarmellose sodium (Endronax and Regenesisc) or sodium starch glycolate (Arendal) as superdisintegrant. Ostenanf contains cellactose (granules containing 75/25 lactose monohydrate/cellulose powder) as the main excipient; sodium starch glycolate is used as disintegrant and the tablets have a red film coat of Eudragit/polyethylene glycol. Excipient information was not available for the other copies studied.

Table 1. Alendronate-containing copies by country

Country	Product name	Manufacturer	City
Argentina	Arendal	Armstrong Syncro S.A.C.I.F	Capital Federal, Buenos Aires
	Regensis	Laboratorio ELEA S.A.C.I. F. y A.	Buenos Aires
Brazil	Endronax	Solvay Farma Ltda (ex. Laboratorios Sintofarma)	São Paulo-SP
	Ostenan	Marjan Indústria e Comércio Ltda	Santo Amaro-São Paulo
Chile	Fosval	Laboratorios Saval S.A.	Santiago
Costa Rica	Osteomax	Manufactured by Laboratorios Stein, S.A., for Gynopharm S.A.	San José
Colombia	Neobon	Manufactured by Procaps S.A. for Gynopharm S.A.	Barranquilla
Ecuador	Fixopan	Manufactured by Laboratorios Farma, S.A., distributed by Laboratorios NOVAPHARMA	Caracas
	Osteomix	Laboratorios Life	Quito
	Osteoplus	Manufactured by Farmacid S.A. for Pharmabrand S.A.	Quito
Peru	Fosmin	Manufactured by D.A.Carrion S.A.C, distributed by REFASA S.A.C.	Lima
Venezuela	Defixal	Linea Megat Pharmaceutical Grupo Leti, S.A.V.	Caracas
	Genalmen	Manufactured by Laboratorios Leti, S.A.V., for Laboratorios Gentek, C.A.	Caracas

Disintegration vs Dissolution

Disintegration refers here to the physical process by which a tablet breaks down into fine particles. This process is monitored visually and pertains to the physical integrity of the tablet alone. Dissolution is the process by which the active ingredient is dissolved into the liquid assay medium. Dissolution is monitored via chemical analysis and provides the approximate time required for full solubilization of the drug under the test conditions. For immediate-release (IR) dosage forms such as the copies investigated, disintegration of the tablet is typically required for full dissolution of the drug.

Disintegration Experiments

Disintegration times were measured *in vitro* by the standard United States Pharmacopeia (USP) disintegration method in USP water at 37 °C using the basket-rack assembly without disks for uncoated tablets¹⁷. In short, one dosage unit was placed in each of the six tubes of the basket-rack assembly and the apparatus was operated. The time required for full disintegration was recorded for each individual unit. The USP definition of disintegration is 'that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core'¹⁷. In these experiments, all tablet cores disintegrated into fine particles which fell through the mesh. For the liquid-filled softgel capsule Neobon, disintegration times reported here represent the time at which the first sign of capsule shell rupture and release of the liquid contents was observed. In most cases, the capsule shells remained on the screen of the apparatus

as a soft, sticky material. At least 12 ($n = 12$) dosage units were tested for each product (except Fosmin⁸, $n = 10$). For some copies, more than one lot was tested to assess lot-to-lot variability. FOSAMAX 70 mg tablets were used as reference.

Dissolution Experiments

The alendronate dissolution profile of Regensis 70 mg, one of the slow-disintegrating copies, was evaluated and compared to that of FOSAMAX 70 mg tablets. Testing was conducted using the Hansen dissolution apparatus (SR 8 Model) fitted with two paddles, operated at 50 rev/min. The dissolution medium was 900 ml of distilled water maintained at 37 °C. Samples were withdrawn with an autosampler at pre-determined time intervals (2, 5, 10, 15, 20, and 30 min) without medium reposition. High Performance Liquid Chromatography (HPLC) following 9-fluorenylmethylchloro-formate (FMOC) pre-column derivatization of alendronate¹⁸ was used for quantification. All calculations were performed with medium volume correction.

Results

The disintegration times for FOSAMAX 70 mg tablets and the copies tested (except Arendal, discussed further below) are shown in Tables 2–6. The lot numbers, number of dosage units tested within each lot, and values for fastest and slowest disintegration times are also provided (Tables 2–6). Figures 1 and 2 show the mean disintegration times for the copies relative to that of FOSAMAX. The error bars represent the range of disintegration times observed for the tablets.

Table 2. Disintegration times (in seconds) for FOSAMAX 70 mg tablets lot E-10129 measured on 4 days

	FOSAMAX (day 1)	FOSAMAX (day 2)	FOSAMAX (day 3)	FOSAMAX (day 4)	FOSAMAX (overall)
<i>n</i> *	4	12	8	3	27
Average time (s)	79.7	88.7	86.2	83.7	86.1‡
Standard deviation	1.6	12.1	13.7	14.6	11.8
% RSD†	2.0	13.6	15.9	17.4	13.7
Slowest time	81.3	106.3	109.7	99.0	109.7
Fastest time	78.0	71.0	72.6	70.0	70.0

*Number of dosage units tested; †relative percent standard deviation; ‡value adopted as reference and used in Figures 1 and 2

Table 3. Disintegration times (in seconds) for the fast-disintegrating copies of FOSAMAX 70 mg

Product	Fosval	Osteoplus	Fixopan	Osteomix	Genalmen	Endronax	Osteomax	Fosmin	Defixal	
Lot	44602	2AJ0404	111529	01-4329	109210	107380	4414	149G1	002492	L001
<i>n</i> *	12	12	14	12	8	4	12	13	10	12
Average time (s)	6.9	14.7	16.2	22.4	26.1	19.5	32.8	44.2	46.5	46.5
Standard deviation	1.5	1.6	2.1	2.1	1.9	3.1	4.7	3.7	11.6	4.4
% RSD†	22.5	10.9	13.0	9.3	7.3	15.9	14.5	8.3	25.0	9.5
Slowest time	9.0	16.0	21.0	25.0	30.1	24.0	40.3	52.0	73.0	54.8
Fastest time	5.0	11.5	12.3	18.2	24.0	17.0	25.0	37.0	34.3	39.4

*Number of dosage units tested; †relative percent standard deviation

Table 4. Summary of disintegration times (in minutes) for Ostenan 70 mg

	Ostenan	Ostenan	Ostenan	Ostenan
Lot	0651	2383	0278	Overall
<i>n</i> *	8	4	2	14
Average time (min)	31.0	14.8	21.5	25.0
Standard deviation	10.4	7.1	0.9	11.2
% RSD†	33.6	48.0	4.4	44.8
Slowest time	46.5	25.3	22.2	46.5
Fastest time	11.9	10.3	20.9	10.3

*Number of dosage units tested; †relative percent standard deviation

Table 5. Summary of disintegration times (in minutes) for Regensis 70 mg

Product	Regensis	Regensis	Regensis	Regensis
Lot	L6857	L7302	L6778	Overall
<i>n</i> *	8	8	4	20
Average time (min)	13.1	12.7	13.2	13.0
Standard deviation†	2.2	1.7	0.8	1.7
% RSD†	16.4	13.2	6.3	13.1
Slowest time	16.1	15.4	14.3	16.1
Fastest time	10.3	10.1	12.5	10.1

*Number of dosage units tested; †relative percent standard deviation

Table 6. Summary of disintegration times (in minutes) for Neobon 70 mg

Product	Neobon	Neobon	Neobon
Lot	2094178	2010217	Overall
<i>n</i> *	17	6	23
Average time (min)	9.3	23.7	13.0
Standard deviation	1.5	2.7	6.7
% RSD†	20.0	22.0	51.4
Slowest time	12.2	27.6	27.6
Fastest time	5.2	20.0	5.2

*Number of dosage units tested; †relative percent standard deviation

FOSAMAX 70 mg

Disintegration times were measured on 4 separate days. The mean disintegration times for each day were 79.7 ($n = 4$), 88.7 ($n = 12$), 86.2 ($n = 8$), 83.7 ($n = 3$) seconds, respectively (Table 2), suggesting good day-to-day consistency. The overall mean disintegration time of all measurements (86 s) was used as the reference for comparison.

Copies

The copies were classified into two groups: those that disintegrated faster and those that disintegrated slower than FOSAMAX.

Copies that Disintegrated Faster than FOSAMAX

The products in this group disintegrated approximately two- to ten-fold faster than FOSAMAX and included Osteomax^h, Defixalⁱ, Fosmin, Endronax, Osteomix^j, Genalmen^k, Fixopan^l, Osteoplus^m, and Fosvalⁿ (Table 3; Figure 1). The mean disintegration times ranged from 6.9 to 46.5 s, with small absolute intra-lot variability. Two lots were available for the copy Genalmen; there was a negligible difference in the mean disintegration time from lot to lot and the overall mean was used in Figure 1.

Copies that Disintegrated Slower than FOSAMAX

The products in this group disintegrated greater than 5-fold slower than FOSAMAX 70 mg (Tables 4–6; Figure 2). Ostenan, a red film-coated tablet, was the

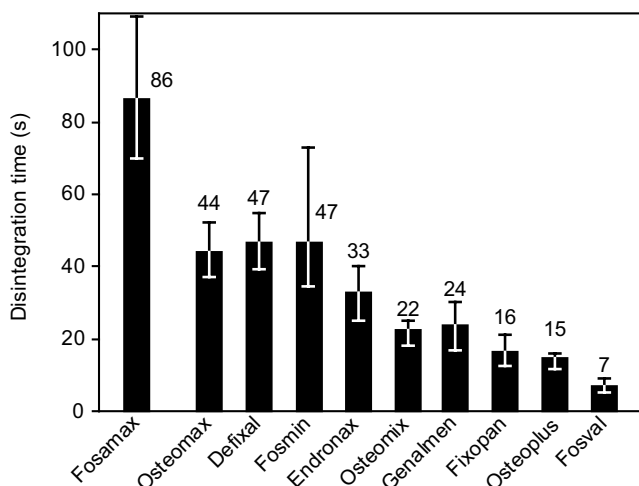


Figure 1. Disintegration times in water at 37°C of copies that disintegrated faster than FOSAMAX 70 mg. Error bars represent the range of individual values measured. For Genalmen, the overall mean was plotted (see Results section)

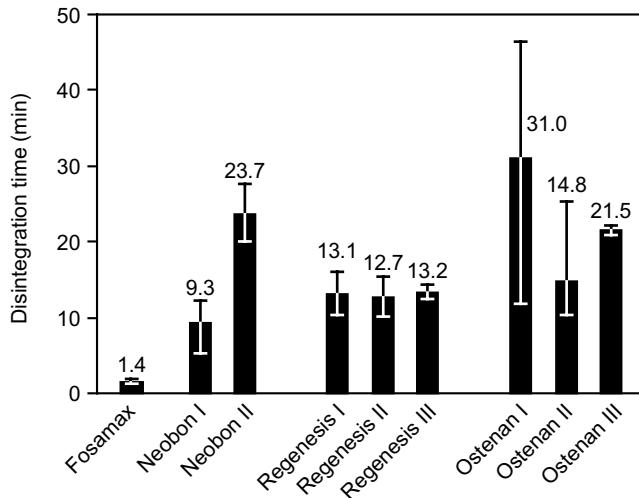


Figure 2. Disintegration times in water at 37°C of copies that disintegrated slower than FOSAMAX 70 mg. Error bars represent the range of individual values measured. See Methods section for details on Neobon measurements

slowest product, ranging from 10.3 to 46.5 min for full disintegration with relatively large intra- and inter-lot variability (Table 4; Figure 2). Regensis, an uncoated compressed tablet, yielded disintegration times ranging from 10.1 to 16.1 min, with minimal inter-lot variability (Table 5; Figure 2). The mean disintegration times for two lots of Neobon, a softgel capsule, were 9.3 min ($n = 17$) and 23.7 min ($n = 6$) (Table 6; Figure 2). As stated previously, the reported times for Neobon correspond to the first observation of liquid contents release into the assay medium. The time for complete release was difficult to assess, but was estimated to take an additional 2–3 min, on average.

Arendal: a Case of Potential High Intra-Lot Variability

The disintegration times for Arendal presented a unique case among the copies tested. Although the mean disintegration times for two lots of this product were not very different from that of FOSAMAX, sporadic but very large intra-lot variability was noted. For instance, tablets from lots S748 P027 and P009 S7603 yielded mean disintegration times of 2.1 min ($n = 16$) and 1.6 min ($n = 7$), respectively, i.e. not much different than FOSAMAX. However, one tablet from the latter lot had a disintegration time of 12.2 min. Moreover, earlier measurements of an unrecorded lot of Arendal during the preliminary stage of this study yielded disintegration times ranging from 8.5 to 11.5 min ($n = 4$). The five abnormally slow disintegrating tablets were excluded from the means given above, but suggest a potentially high variability in the disintegration profile of this product.

Dissolution Test

The dissolution of alendronate from Regenesis lagged behind that from FOSAMAX (Figure 3). For example, > 90% alendronate dissolved from FOSAMAX after only 5 min, with full dissolution (approximately 95% of the 70 mg amount stated on the label) well before 10 min under the experimental conditions. In contrast, only 80% alendronate dissolved from Regenesis after 20 min, and it took as long as 30 min to reach approximately 88%. This delayed dissolution profile is qualitatively consistent with Regenesis' prolonged disintegration time described above.

Discussion

The present study identified two groups of copies: very fast- and very slow-disintegrating. The different disintegration times of these copies could alter the clinical efficacy and safety profiles relative to original FOSAMAX 70 mg.

Bioavailability

Bioavailability is the degree of activity or amount of an administered drug or other substance that becomes available for activity in the target tissue. Thus, alterations in the bioavailability of a drug may reduce efficacy or result in a toxic effect. Absorption of alendronate occurs in the upper gastrointestinal tract, and bioavailability is quite low (typically less than 1% on average), even on an empty stomach. Bioavailability of oral bisphosphonates is negligible in the presence of food, even if administered up to 2 h after a standard breakfast, and is substantially impaired when taken concomitantly with coffee or orange juice^{19,20}. For that reason, dosing instructions for most bisphosphonates (including FOSAMAX) require a 30-min fasting period post-dose to ensure adequate bioavailability¹¹. It is also possible that differences in disintegration or dissolution times relative to FOSAMAX may influence the bioavailability and pharmacokinetics beyond the potential food effect. Moreover, the bioavailability may be altered as other characteristics of the tablet are altered, such as the type of excipient.

Efficacy

The slower times associated with the full disintegration of Neobon, Regenesis and Ostenan tablets, and thus the delayed release of alendronate, increases the likelihood that an incompletely disintegrated tablet, prior to full release of drug, would also come into contact with

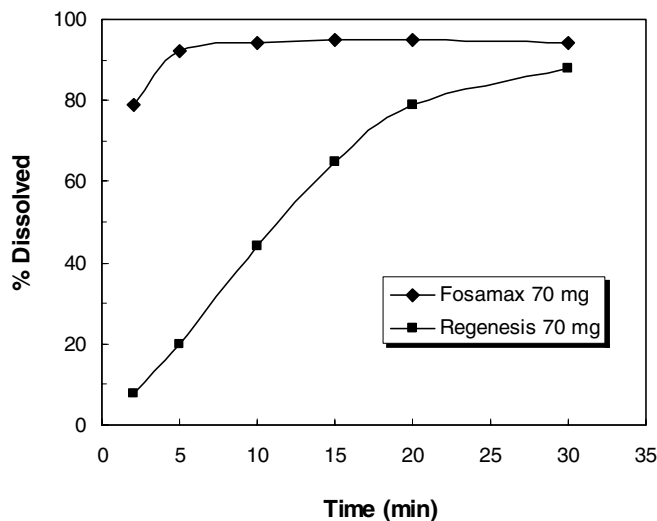


Figure 3. Alendronate dissolution profiles of Regenesis 70 mg and FOSAMAX 70 mg, expressed as % of the amount (70 mg) stated on the label

subsequently ingested food, mucus, or liquids. Considering the dosing instructions, such a scenario is more likely with products having longer disintegration times (e.g. > 30 min), such as Ostenan in the present study. The slower dissolution of Regenesis suggests that even those products with disintegration times that are less than 30 min, but still considerably longer than FOSAMAX, would not necessarily display *in vivo* bioavailability and pharmacokinetic properties comparable to FOSAMAX.

The faster disintegration times relative to FOSAMAX 70 mg, as observed with Osteomax, Defixal, Fosmin, Endronax, Osteomix, Genalmen, Fixopan, Osteoplus, and Fosval, could result in reduced efficacy for the following reason: premature disintegration may be associated with semi-particulate alendronate matter being retained within the esophagus, increasing the likelihood of contact with ingested food, saliva, mucus or liquids, thereby reducing bioavailability or altering the pharmacokinetics.

Safety

Bisphosphonates have the potential for esophageal irritation and injury^{12,21}, although the upper gastrointestinal safety profile of FOSAMAX in randomized controlled trials is similar to placebo^{3-10,15}. The dosing instructions for FOSAMAX (to wash the tablet down with a glass of water and remain upright for at least 30 min) are designed not only to enhance bioavailability, but also to ensure that the tablet clears the esophagus quickly in order to minimize the potential for esophageal irritation. The short times associated with the disintegration of several alendronate-containing copies were mostly in the 15-47 s range, but as fast as 7 s for Fosval. For these products, there is a chance that disintegration may occur in the mouth and/or the

esophagus during swallowing of the tablet. This could increase the duration and extent of oral and esophageal tissue exposed to semi-particulate alendronate, and thereby increase the risk of serious mucosal irritation and ulceration.

Pill esophagitis has been reported with bisphosphonates, especially when dosing instructions are not followed²¹. An important mechanism is believed to be prolonged contact with the esophageal wall^{21,22}, which may be influenced by several factors, including delayed esophageal transit and formulation characteristics²³. A product with slower disintegration or dissolution times might be more prone to 'pill esophagitis', particularly in patients with asymptomatic, subclinical esophageal diverticuli, rings, or motility disorders that delay esophageal transit. For example, esophagitis was reported in a previous trial of risedronate using a delayed-release tablet formulation of the 30 mg Paget's disease dose, which was subsequently abandoned in favor of an immediate-release formulation²⁴. Also, in the event that a patient with esophageal reflux disease does not follow dosing instructions strictly and lies down sooner than 30 min or before eating, delayed disintegration would make it more likely that a partially disintegrated tablet could be refluxed into the esophagus, increasing the likelihood of adverse events.

Certain features of the drug formulation that were not evaluated in this study may predispose patients to esophageal injury by delaying esophageal transit, including tablet size, density, shape, and coating^{25,26}. For instance, data from animal models and clinical studies using radioactive imaging techniques have shown that gel capsules have a greater tendency to adhere to esophageal mucosa compared with tablets, resulting in longer esophageal transit times²⁷⁻²⁹. An early trial involving evening dosing with pamidronate gel capsules reported severe upper gastrointestinal adverse events³⁰, and recent bisphosphonate programs have avoided the use of gel capsules. This raises additional safety concerns with regard to the Neobon gel capsule, beyond the long disintegration times measured. Even though disintegration times *in vivo* might differ from those measured by the USP method, the problems encountered earlier with pamidronate gel capsules suggest that clinical studies are warranted to evaluate the safety profile of alendronate formulated as a gel capsule such as Neobon.

The Unique Disintegration Behavior of Arendal

Arendal was unusual in that the overall mean for two lots tested was not much different from FOSAMAX when outliers were excluded (total $n = 23$), but relatively large variability was recorded for a few of the

tablets. The observation of long disintegration times of 8.5–12.2 min for five tablets raises the possibility of high inherent variability which could have important adverse effects on the clinical efficacy and safety. Whether or not the sporadic variability observed is representative across a lot cannot be concluded from these data, but it certainly raises a concern regarding uniform tablet quality.

Limitations

The results reported here represent a limited sample of tablets and gel capsules from only one or two lots of each copy. It is unknown whether these results are representative of other lots. Nevertheless, most of the samples tested had disintegration times which were much faster or slower than FOSAMAX. Moreover, with one exception (Regenesis), we did not evaluate how much alendronate was contained in each tablet or gel capsule. Even if the actual amounts agree well with the stated amounts (70 mg alendronate), the dissolution and pharmacokinetic profiles of these copies are unknown, and could vary depending on excipients or other factors¹. Our findings raise important questions, and suggest that copies should not be considered equivalent to FOSAMAX until further investigations have been conducted.

The disintegration/dissolution profiles *in vivo* may differ from those reported here. For example, it is possible that the disintegration of an Ostenan tablet in the stomach's acidic environment may be different than that measured by the USP method in water, because the Eudragit/polyethylene glycol coating of Ostenan seems to degrade faster in acidic solution. That difference notwithstanding, the tablet coating constitutes a major formulation change that could alter the pharmacokinetic properties. The safety and bioavailability of a tablet with an acid-sensitive coating has not been validated in clinical studies to our knowledge, and cannot be assumed to remain unchanged with respect to the uncoated tablets.

Although prior research suggests that the observed differences in disintegration and dissolution might affect the clinical efficacy and safety profiles of copies relative to FOSAMAX, the magnitude and extent of such effects remains uncertain. In view of these uncertainties, further research is warranted to evaluate the pharmacokinetic and safety profiles of copies to determine if they are therapeutically equivalent to FOSAMAX.

Conclusions

The copies tested in the present study disintegrated at very different rates than that of original FOSAMAX

70 mg. Previous research on alendronate and other bisphosphonates predicts that differences in disintegration/dissolution could potentially reduce bioavailability and efficacy relative to FOSAMAX. Moreover, longer or shorter disintegration times could potentially increase the risk of esophagitis by mechanisms outlined above. Other factors which were not evaluated in the current study could also affect bioavailability and safety profiles. Therefore, further research, possibly including pharmacokinetic and clinical safety studies, is warranted before these copies can be deemed to be 'therapeutically equivalent' to FOSAMAX.

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