Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Alendronic acid

Proprietary Product Name: Alendraccord, Alendrocor, Pharmacor Alendronate

Sponsor: Accord Healthcare Pty Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Generic
Decision:	10 mg strength approved 70 mg strength rejected
Date of Decision:	10 mg: Approval: 20 September 2010 70 mg: Initial rejection: 7 September 2010 70 mg: Final rejection: 1 February 2011
Active ingredient(s):	Alendronic acid (as alendronate sodium)
Product Name(s):	Alendraccord, Alendrocor and Pharmacor Alendronate
Sponsor's Name and Address:	Accord Healthcare Pty Ltd Unit 702, 23 Queens Road Melbourne Vic 3004
Dose form(s):	Tablet
Strength(s):	10 mg and 70 mg
Container(s):	Blister packs
Pack size(s):	10 mg: 30
Approved Therapeutic use:	For the treatment of osteoporosis*. For treatment and prevention of glucocorticoid-induced osteoporosis in post menopausal women not receiving oestrogen and who are on long term corticosteroid therapy. *Prior to treatment, osteoporosis must be confirmed by the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults or by the presence of osteoporotic fracture.
Route(s) of administration:	Oral
Dosage:	10 mg: once daily
ARTG Number (s)	161444, 161445 and 161448

Product Background

Alendronic acid (as sodium alendronate) has been registered in Australia and elsewhere for many years. The innovator product is Fosamax and there are a number of generic versions on the Australian Register of Therapeutic Goods (ARTG). Fosamax is available in a number of presentations and it is indicated for the treatment of osteoporosis (in 5 mg, 10 mg and 70 mg presentations) and treatment and prevention of glucocorticoid-induced osteoporosis in those patients on long term corticosteroid therapy (5 mg) and treatment and prevention of glucocorticoid-induced osteoporosis in post menopausal women not receiving oestrogen and who are on long term corticosteroid therapy (10 mg). It is also approved for treatment of Paget's disease.

This is an application for the registration of generic sodium alendronate tablets in 10 mg and 70 mg strengths, with two additional trade names. Thus, there are three trade names proposed

- Alendraccord, Alendrocor and Pharmacor Alendronate – but the product will be referred to as Alendraccord for the remainder of this document. Proposed indications in the draft product information (PI) are:

*Alendraccord 70 mg is indicated for the treatment of osteoporosis**

Alendraccord 10 mg is indicated for the treatment of osteoporosis.*

Alendraccord 10 mg is also indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in postmenopausal women not receiving oestrogen and who are on long-term corticosteroid therapy.

*'*Prior to treatment, osteoporosis must be confirmed by:*

The finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults

or by the presence of osteoporotic fracture.'

There are no 5 mg tablets proposed for registration, thus the prevention indication for glucocorticoid-induced osteoporosis is restricted to women not taking oestrogen.

Regulatory Status

A similar application was approved in August 2008 in 16 European countries, including Germany, Sweden, the Netherlands and the UK, under the decentralised procedure. The product is presented as 10 mg and 70 mg tablet strengths in Europe. An application is under review in Canada.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. Only the PI for Alendraccord is attached; those for Alendrocor and Pharmacor Alendronate are essentially identical.

II. Quality Findings

Introduction

Applications for new generic medicines usually require evaluation for quality control and chemistry and a study to show bioequivalence with the innovator brand. In this application there were no outstanding issues with respect to chemistry and quality control.

Biopharmaceutics

Bioavailability

Alendronate is poorly absorbed. The innovator and proposed PIs state that oral bioavailability is about 0.64% (administered fasted and 2 hours before a standardised breakfast) in women and 0.6% in men. Time to maximal plasma concentration (T_{max}) is typically ~ 2 hours and the maximal plasma concentration (C_{max}) is < 5 - 8.4 ng/mL. The bioavailability of alendronate is very low and measurement of plasma levels is unreliable. The drug is eliminated via urine only. Given this, urine is used as the fluid to assess bioavailability.

The bioequivalence study was an open-label, balanced, randomised, single-dose, two-treatment, four-period crossover study. The two dose sequences were BABA and ABAB. Each subject received 70 mg of alendronic acid (1 test or reference tablet) in each of four sessions separated by a wash-out period of 23 days. Subjects were fasted overnight for 10 hours and for 4 hours post-dose (further meals were given after this time). The 70 mg tablet dose was administered with 240 mL water in a sitting posture in each period.

Urine samples were collected pre-dose and for 36 hours post-dose during each session

The 90% confidence intervals (CI) for the observed maximum excretion rate (R_{max}) and the cumulative amount of drug measured in the urine from time zero to 36 hours (Ae_{0-36}) for the test product versus the reference product were within the range 0.80 - 1.25 for alendronic acid as required to conclude bioequivalence. The 90% confidence intervals for R_{max} spanned unity. The 90% confidence interval for Ae_{0-36} did not span unity and the point estimate. This was brought to the attention of the Delegate.

Justification for not submitting a study on the 10 mg tablets

The sponsor stated that tablet cores for the 10 mg and 70 mg presentations are direct scales. The drug is not metabolised, the 70 mg presentation is bioequivalent to the innovator product, the drug is soluble in water and acid, the drug is eliminated via the urine and urinary recovery is linear over the dose range 5 - 80 mg, the 10 mg dose has been shown to product a clinically significant effect and doses higher than 70 mg have been found to be well tolerated. The justification was considered acceptable on pharmaceutical grounds.

Quality Summary and Conclusions

There were no outstanding issues with respect to chemistry and quality control.

Although the product can be formally considered bioequivalent to the Australian innovator product, the 90% confidence intervals for the amount of drug in the urine (Ae) did not span unity for alendronic acid and the point estimates suggest that the extent of elimination of the test product is approximately 10% more than that of the reference product. Clinical comment was requested on this issue.

A justification for not submitting bioequivalence data was provided for the 10 mg presentation.

However, the evaluator noted that there were serious clinical concerns in relation to the large size of the proposed 70 mg tablet and these were referred to the Delegate.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The clinical aspect of the submission rests on a claim of essential similarity, based on the demonstration of bioequivalence of the sponsor's 70 mg sodium alendronate tablet to the innovator alendronate 70 mg tablet. The clinical submission included a report of a bioequivalence study of the 70 mg sodium alendronate test tablet (Intas) against a 70 mg reference alendronate tablet (Fosamax). The reference tablet is Fosamax 70 mg tablets sourced from Merck Sharp & Dohme Pty Ltd Australia. The test tablet is alendronate sodium tablets 70 mg, Intas Pharmaceuticals Ltd., India. The TGA-adopted European Union (EU) guidance on investigation of bioavailability and bioequivalence are stated to have been followed in planning the single dose study in healthy men.[1] The certificates of analysis of the test and reference products show that although the excipients are qualitatively similar to the

[1] EMEA. Committee for Proprietary Medicinal Products (CPMP), 26 July 2001. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. CPMP/EWP/QWP/1401/98. http://www.tga.gov.au/docs/pdf/euguide/ewp/140198entga.pdf

innovator tablets, the average weight of the reference product tablet is 356 mg while that of the test product is 773 mg; tablet dimension specifications were not located.

A justification for not conducting a bioequivalence study with the 10 mg tablets is provided in Section II. This is based on the tablets having the same manufacturing process and site, linear pharmacokinetics *(*PK) for alendronate over the dose range, dose proportionality of the 10 mg formulation to the 70 mg formulation*,* comparable dissolution profiles, and the known adverse effect (AE) profile of alendronate, with discontinuations due to AEs uncommon.

Pharmacokinetics

Introduction

One bioequivalence (BE) study, Project 282-07, was conducted. It was an open label, balanced, randomised, single dose, two-treatment, four period, replicate, two-sequence, two-way crossover oral bioequivalence study of sodium alendronate tablets 70 mg (test product, B) in comparison with Fosamax 70 mg tablets (reference product, A) in 120 healthy adult men under fasting conditions.

Subjects were males aged 18-55 years with no significant diseases or clinically significant abnormal findings at screening, medical history, physical examination and laboratory evaluations. Exclusion criteria included known hypersensitivity or idiosyncratic reaction to alendronate or related drugs, any condition compromising any body system, concomitant medication 14 days prior to dosing, smoking >10/day or drug use, other investigational drug ingestion within 90 days prior to first dose.

Because of low oral bioavailability and known difficulties in measuring plasma alendronate, this study measured urine alendronate as discussed in Section II.

Sample size calculations were based on an in-house pilot study which found the maximum intra-subject variability to be 48%. It was calculated that doubling the number of measurements would reduce the intra-subject variability to 34%. Therefore the following estimates were used for computation of sample size: Test/reference ratio 90-110%; Significance level=5%; Power > 80%; Bioequivalence limits 80-125%. Based on these considerations, 100 subjects were sufficient; 124 were initially enrolled and 120 subjects dosed in Period 1.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated from the drug concentration-time profile by a non-compartmental model for alendronic acid. Descriptive statistics were computed and reported for all PK parameters of alendronic acid. The parameters were to be derived individually for each subject from the concentration vs. time profiles of alendronic acid in urine.

Statistical analysis

Statistical analysis was to be performed on data from subjects completing all four treatment periods or at least the first two periods with no significant protocol deviations.

Statistical comparisons of the PK parameters of the two formulations were carried out to assess bioequivalence of alendronic acid. Analysis of covariance (ANCOVA), two one sided tests for bioequivalence, power and ratio analysis for ln-transformed pharmacokinetic parameters maximum observed excretion rate (R_{max}), area under urinary excretion rate curve from time zero to last measurable rate ($AURC_{last}$), and area under urinary excretion rate curve extrapolated to infinity ($AURC_{\infty}$) computed for alendronic acid, and the 90% parametric CI, were computed for these parameters for alendronic acid.

Absorption

Bioavailability

Relative oral bioavailability of alendronate is known to be very low (0.64% /0.76% for women for doses 5 to 70/80 mg administered after an overnight fast and two hours before a standard breakfast, 0.6% in men) (2). There is known to be substantial within and between subject variability in oral absorption (63% and 77% respectively) (Fosamax PI).

Subjects were randomised to the 4 period crossover sequence (either ABAB or BABA).

Subjects fasted overnight for 10 hours and then were administered one tablet of either reference (A) or test (B) treatment orally with 240 mL of water in the sitting posture in each period, remaining upright for the first three hours after dosing. Urine samples were collected in 11 pre-specified collection intervals in each period until 36 hours post dosing.

The mean untransformed PK parameters of alendronic acid for Reference-A and Test-B in 114 subjects are summarised in Table 1.

Table 1: PK parameters

Parameters(units)	**Mean (SD) untransformed data**	
	Reference (A)	Test (B)
$T_{max\_\ Rate}$ (h)#	1.5 (# median)	1.5 (# median)
R_{max} (mL*ng/mL/h)	87592.798(66811.3071)	88610.250(58291.7460)
$AURC_{last}$ (mL*ng/mL)	229539.198(158177.3840)	258307.701(180108.6515
$AURC_{\infty}$ (mL*ng/mL)	236312.487(162293.8820)	265688.887(182553.6234)
λ_z (1/h)	0.138(0.0840)	0.135(0.0757)
$t_{½}$ (h)	6.992(4.1742)	7.034(4.3738)
AURC_% Extrap_Obs(%)	3.087(2.0304)	3.162(2.2383)

$T_{max\_\ Rate}$: midpoint of collection interval associated with maximum observed excretion rate
λ_z: terminal rate constant, estimated via linear regression of midpoints vs. log excretion rates
$t_{½}$: elimination half-life, calculated as $0.693/\lambda_z$
AURC_%Extrap_Obs: % of the area under the curve that has been derived after extrapolation of % Residual Area

Comment

The urinary alendronate excretion estimates are comparable to those in other studies of single oral doses of 70 mg alendronate tablets, noting that there is wide variability in both measured alendronate urinary excretion and bioavailability calculated from these parameters.

Bioequivalence

Project 282-07

Based on the statistical results of the 90% confidence interval for the ratio of geometric least squares mean for the ln-transformed PK parameters R_{max}, $AURC_{last}$, and $AURC_{\infty}$, bioequivalence of test product B versus reference product A would be concluded if the 90% CI falls within the acceptance range of 80-125% for these parameters.

Comparisons and statistical analyses are shown in Table 2.

Table 2: Comparisons and statistical analyses for Project 282-07

Parameters(units)	ln-transformed Geometric Least Squares Mean			90% Confidence intervals (parametric)	Intra-subject CV(%)
	Test Product B	Reference Product A	Ratio (B/A) %		
R_{max} (mL*ng/mL/h)	73003.869	70239.278	103.9	96.81-111.59	A 50.8 B 39.9
$AURC_{last}$ (mL*ng/mL	207129.392	187308.128	110.6	102.42-119.39	A 47.5 B 43.8
$AURC_{\infty}$ (mL*ng/mL)	213949.772	193042.704	110.8	102.77-119.53	A 47.9 B 43.2

Thus the 90% CI fell within the acceptance limits of 80-125% required for bioequivalence as set out in the protocol, for all three pre-specified parameters.

Significant period effects found by ANOVA for R_{max} were attributed to the washout period of 23 days. Significant formulation effects found by ANOVA were attributed to the high B/A ratios and intra-subject coefficient of variation (CV%) for the AURC data.

Comment

The subject CV% observed for the maximum excretion rate was not substantially lower for the test product than in the pilot study, although that for the reference product approached the 34% predicted for this replicate study when sample size was calculated.

Influence of food

The study was conducted in fasting subjects. A standard meal was provided 4 hours after dosing.

It is known that bioavailability is negligible if alendronate is administered with or up to two hours after a standardised breakfast.

Elimination

Excretion

Alendronate urinary excretion rates were used to estimate the bioavailability of the oral dose and as the basis for calculating parameters for assessing bioequivalence.

Metabolism

Alendronate is not appreciably metabolised in the liver.

Dose proportionality and time dependency

Dose proportionality

The data provided were for the highest strength proposed for registration, 70 mg tablets. The Innovator PI and the quality section of this submission both state 'Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast'.

Intra- and inter-individual variability

The innovator PI and the quality section of this submission both state 'There was substantial variability both within and between patients, coefficient of variation 63% and 77%, respectively'. In this replicate crossover BE study Project 282-07, the intra-subject CV for all primary pharmacokinetic parameters was > 30%. Linear plots of individual urine concentration versus time curves show the expected high variability for such measurements.

Pharmacokinetics in the target population

No data was provided from patients with osteoporosis; the BE study was conducted in healthy men.

Exposure relevant for safety evaluation

There were 120 subjects dosed in period 1, 114 in period 2, 99 in period 3 and 91 in period 4, all of whom contributed to safety data. There were no appreciable differences in characteristics of those who completed all 4 single dose periods compared to those who commenced in Period 1.

Evaluator's overall conclusions on pharmacokinetics

Alendronate has low oral bioavailability; approximately 0.64% in women over the dose range 5 to 70 mg, 0.6% in men. Because of this, and known difficulties in measuring plasma alendronate, this study measured urine alendronate concentration over 36 hours post-dose as a measure of absorption in study subjects. The sample size of 120 was considered adequate in view of the replicate study design. Comparisons and statistical analyses are shown in Table 2. Based on the statistical results of the 90% confidence interval for the ratio of geometric least squares mean for the ln-transformed PK parameters R_{max}, $AURC_{last}$, and $AURC_{\infty}$, bioequivalence of test product B vs. reference product A was concluded because the 90% CI fell within the acceptance range of 80-125% for the parameters specified in the protocol.

While the criteria for bioequivalence are satisfied by the calculations resulting from the study, it is noted that the tablet proposed for registration is approximately double the weight of the innovator tablet. Overall there is a higher excretion of alendronate after a single 70 mg tablet of the test product proposed for registration than after a single 70 mg tablet of Fosamax.

The high CV% and the high B/A ratio were given as the reasons for the formulation effect shown by ANOVA of the ln-transformed data. Although the low oral bioavailability and high variability of alendronate suggest that these observations may not have clinical significance, they were drawn to the attention of the quality evaluator for comment. Additionally, comment was requested on the significantly different weight of the 70 mg test tablet compared to the 70 mg reference tablet, and the potential for local adverse effects (oesophageal) if this reflects a larger dimension tablet (see *List of Questions*).

The justification for not undertaking a bioequivalence study with the 10 mg tablet is acceptable, due to the low oral bioavailability of the drug and its skeletal sequestration. Adverse events are now well known, are adequately described in the PI and are not more likely with the lower strength.

Pharmacodynamics

There were no pharmacodynamic data provided.

Efficacy

There were no studies of clinical efficacy provided. Clinical efficacy is claimed to be similar to the innovator alendronate tablets (Fosamax), through the single bioequivalence study provided.

In general the evaluator considered that it is reasonable to include a summary of the bioequivalence study in the PI because this is the clinical information that justifies the claim of bioequivalence.

Safety

Introduction

Clinical safety of this product is expected to be the same as for the innovator Fosamax. Significant adverse events reported with alendronate tablets include gastrointestinal (GI) disorders (for example, oesophagitis and abdominal pain), muscle and bone pain, headache, and rarely hypocalcaemia, osteonecrosis of the jaw and severe skin reactions. The potential for upper GI adverse effects is minimised by the instruction to remain upright for at least 30 minutes after swallowing the tablet with water; alendronate is contraindicated in delayed oesophageal emptying, inability to remain upright after dosing, and hypocalcaemia. The dosing instructions were strictly followed in this bioequivalence study.

Therapeutic equivalence also implies equivalent safety, which for alendronate requires assessment of local GI irritation, probably unrelated to bioavailability. A potential problem is that differences in formulation or tablet characteristics may increase the likelihood of local GI irritation.

Patient exposure

There were 120 subjects dosed in Period 1, 114 in Period 2, 99 in Period 3 and 91 in Period 4, all of whom contributed to safety data.

Adverse events

A total of 48 adverse events were reported during the conduct of the trial. All were mild except for one subject reporting moderate itching. This event required multiple treatments including dexamethasone injection and the patient was withdrawn; it occurred 21 days after dosing and was considered unlikely related to the study drug.

Other events considered possibly related were

- "bodyache" (test product B, n =2)
- epigastric pain (test product B, n=1, 3 days after study drug administration; a second report for test product B, in period 2 on the second day after dosing, was considered unlikely related even though it appeared to be in closer temporal proximity to study drug administration than the former event)
- right sided muscular chest pain (test product B, n= 1)
- abdominal pain (n = 2 reference product A)
- headache (n = 1, reference product A)

Serious adverse events and deaths

There were no deaths or other serious adverse events.

There were 7 events considered to be significant; accidental injury (n = 3), itching with rashes, herpes progenitalis, chancroid and chickenpox (all n = 1), all considered unrelated or unlikely related.

Laboratory findings

Of the out-of-range laboratory values, none were considered to represent clinically significant abnormalities.

Vital signs

There were no clinically significant abnormalities detected during the dosing and urine collection periods.

Discontinuation due to adverse events

There were six subjects withdrawn due to significant adverse events, all of which were considered unlikely to be related to study drug.

Post marketing experience

This generic product has been accepted for registration in Europe but no post marketing data were provided.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

Safety

The reference tablet is Fosamax 70 mg tablets sourced from Merck Sharp & Dohme Pty Ltd Australia. The test tablet is alendronate sodium tablets 70 mg, Intas Pharmaceuticals Ltd., India. The certificates of analysis of the test and reference products show that although the excipients are qualitatively similar to the innovator tablets, the average weight of the reference product tablet is 356 mg while that of the test product is 773 mg; tablet dimension specifications were not located. The quality section of the submission contains confirmation that the test product is identical to the subject of the registration application.

Adverse events included two reports of epigastric pain for the test product, even though the administration instructions about remaining upright after dosing were strictly adhered to and the subjects were healthy with no known history of oesophageal disease. This raises concerns about differences in physical characteristics, such as shape and size of the tablets proposed for registration compared to the innovator, and the potential for oesophageal irritation.

The quality evaluator has provided the following comments on tablet dimension:

"During the formulation development the sponsor made 10 mg tablets weighing 110 mg (3.13 - 3.18 mm thick and 3.60 - 3.65 mm thick) with similar dissolution to the innovator. The in-process control limits thickness of the product to 2.70 - 3.10 mm and weight to 104.5 - 115.5 mg.

The sponsor made 70 mg tablets weighing 770 mg (6.40 - 6.43 mm thick) and 70 mg tablets using a different excipient composition weighing 350 mg (3.87 - 3.88 mm thick, but with dissolution slower than the innovator). The weight of the proposed 70 mg product is 770 mg. The validation data show thickness was approx. 6.4 mm. The in-process control limits thickness of the product to 6.30 - 6.70 mm and weight to 746.9 - 793.1 mg.

No other data were provided in relation to tablet dimensions."

Question

Please provide complete data on the dimensions of the alendronate tablets proposed for registration, and the innovator tablets used in the bioequivalence study.

If the dimensions of test and reference tablets are appreciably different, please comment on this with particular reference to the potential for alendronate to cause oesophageal and other upper gastro intestinal irritation.

Clinical Summary and Conclusions

Pharmacokinetics

Comparisons and statistical analyses are shown in Table 2. Based on the statistical results of the 90% confidence interval for the ratio of geometric least squares mean for the ln-transformed PK parameters R_{max}, $AURC_{last}$, and $AURC_{\infty}$, bioequivalence of test product B versus reference product A was concluded because the 90% CI fell within the acceptance range of 80-125% for the parameters specified in the protocol.

The clinical evaluator was asked to respond to the quality evaluator's comment in relation to the 90% confidence interval for the cumulative amount of drug in the urine. The evaluator noted that although the formal bioequivalence criteria were satisfied, overall the extent of alendronate excretion was higher for the test product by approximately 10%, with the 90% confidence intervals for test: reference ratio lying entirely above unity. Alendronate is characterised by skeletal sequestration of approximately 50% of absorbed dose and is intended for long-term use. Therefore on the available data, the possibility cannot be excluded that for this medicine, that patients changed from the innovator to the generic 70 mg weekly alendronate dose may subsequently have, on average, 10% greater exposure.

Safety

At least 91 patients were exposed twice to single doses of the tablet proposed for registration in the bioequivalence study Project 282-07.

A total of 48 adverse events were reported during the conduct of the trial. All were mild except for one subject reporting moderate itching, considered unrelated due to time elapsed since study drug administration. Events considered related were "bodyache", epigastric pain, muscular chest pain, abdominal pain, and headache, all of which are described in the innovator PI.

There were no serious adverse events or deaths. There were 7 clinically significant events; all considered unrelated or unlikely related.

Of the 7 subjects with clinically significant events, 6 subjects were withdrawn due to the adverse events; 5 were considered unlikely related and one considered unrelated.

The evaluator had some concern that reports of epigastric pain for the test product under strict administration conditions may have been caused by local upper gastrointestinal mucosal irritation, possibly reflecting differences in physical characteristics of the test tablet compared to the reference tablet.

Benefit risk assessment

Benefits

The 70 mg tablet has been shown to meet accepted bioequivalence criteria. The justification for not conducting a bioequivalence study with the lower strength is acceptable. The benefits are expected to be those shown for the innovator if bioequivalence is accepted.

Risks

The risks of adverse effects should be similar to the innovator. However, the alendronate 70 mg tablet proposed for registration is also appreciably larger than the innovator tablet and other registered generic alendronate tablets.

It is not possible to be certain there was equivalent safety or tolerability based on the bioequivalence study.

No post-marketing safety data or Periodic Safety Update Reports (PSURs) were available for the products proposed for registration.

Formulation differences are suggested both by the reported dissolution data and the bioequivalence study. The data are consistent with 10% greater exposure with the new generic alendronate proposed for registration.

Conclusions

Based on the available data, the 70 mg alendronate tablet is not considered to be an equivalent presentation to the innovator although it fulfils the theoretical criteria for bioequivalence.

In view of the lack of clinical data demonstrating equivalent safety in the target population, registration is not recommended for this strength.

V. Pharmacovigilance Findings

There was no requirement for a pharmacovigilance evaluation in a submission of this type.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator noted that the 70 mg tablet has been shown to meet the standard criteria for bioequivalence with the Australian innovator although the 90% confidence intervals for the $A_{e0\text{-}36}$ did not span unity (see below). The evaluator was satisfied with the conduct of and the analytical aspects of the study. The applicant has provided a justification for not conducting a bioequivalence study on the 10 mg strength tablet. On the basis of the pharmaceutical chemistry component of this justification, the results for the 70 mg tablet can be considered applicable to the proposed 10 mg tablet. Clinical concerns were noted by the evaluator, so a limited recommendation has been made which are, confined to satisfactory chemistry and quality control matters.

There were no outstanding issues with respect to chemistry and quality control.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Study 282-07 was an open label, balanced, randomised, single dose, two-treatment, four period, replicate, two-sequence, two-way crossover oral bioequivalence study of sodium alendronate tablets, 70 mg (test product, B) in comparison with Fosamax 70 mg tablets (reference product, A) in 120 healthy adult men under fasting conditions. One hundred and fourteen subjects received at least on dose of both formulations and the results are presented at Tables 1 and 2.

The 90% CI fell within the acceptance limits of 80-125% required for bioequivalence as set out in the protocol, for all three pre-specified parameters, R_{max} (mL*ng/mL/h); $AURC_{last}$ (mL*ng/mL and $AURC_{\infty}$ (mL*ng/mL. Bioequivalence was therefore established.

Significant period effects found by ANOVA for R_{max} were attributed to the washout period of 23 days. Significant formulation effects found by ANOVA were attributed to the high B/A ratios and intra-subject CV% for the AURC data. In this replicate crossover bioequivalence study 282-07, the intra-subject CV for all primary pharmacokinetic parameters was > 30%.

The clinical evaluator noted that the 70 mg tablets are physically much larger than the innovator's.

The evaluator observed, "Therapeutic equivalence also implies equivalent safety, which for alendronate requires assessment of local GI irritation, probably unrelated to bioavailability. A potential problem is that differences in formulation or tablet characteristics may increase the likelihood of local GI irritation."

Submitted safety data relate to the bioequivalence study, not to any post-marketing data. The safety data were unremarkable. However, "Adverse events included 2 reports of epigastric pain for the test product, even though the administration instructions about remaining upright after dosing were strictly adhered to and the subjects were healthy with no known history of oesophageal disease."

Consequently, the evaluator asked for complete data on the relative dimensions of the 70 mg generic and innovator tablets and for comment on the difference in size with particular reference to the potential for alendronate to cause oesophageal and other upper gastrointestinal irritation.

With regard to the 10 mg tablet, it is a direct scale downwards of the 70 mg generic tablet; a justification for not conducting a bioequivalence study with the 10 mg tablets was provided by the applicant. This justification was based on the 10 mg tablets having the same manufacturing process and site, linear pharmacokinetics for alendronate over the dose range, dose proportionality of the 10 mg formulation to the 70 mg formulation, comparable dissolution profiles, and the known adverse effect profile of alendronate, with discontinuations due to adverse events said to be uncommon. The justification for not conducting a bioequivalence study with the lower strength was considered to be clinically acceptable.

Approval was conditional upon resolution of potential safety concerns arising from possible disparity of sizes between the innovator and the proposed 70 mg generic tablet.

Risk-Benefit Analysis

As requested by the clinical evaluator, dimensions of the 70 mg tablet were provided by the sponsor (Table 3).

Table 3: Tablet dimensions

	Test (proposed commercial)	Reference product [Fosamax]
Average weight	770 mg	350 mg
Thickness	6.50mm	4.54 mm
Tablet dimensions	17.3 x 9.20 mm	12.8 x 7.2 mm

The evaluator noted that "this represents an appreciable increase in all dimensions for the generic 70 mg alendronate tablet proposed for registration, compared to the innovator Fosamax. The innovator Fosamax 70 mg tablet is a large tablet when all dimensions are taken into account." The evaluator considered that it is reasonably possible for a larger tablet size to increase the risk of medication related injury to the oesophageal mucosa; several standard sources were cited in support of this belief.

The Fosamax 10 mg tablet is of comparable size and weight to the proposed generic 10 mg tablet.

A residual concern of the evaluator was that the generic formulation was statistically more bioavailable than the 70 mg reference formulation, "Thus although the formal bioequivalence criteria were satisfied, overall the extent of alendronate excretion was higher for the test product by approximately 10%, with the 90% confidence intervals for test: reference ratio lying entirely above unity. Urine excretion is the surrogate marker for alendronate exposure, used because of low measurable bioavailability. Alendronate is characterised by skeletal sequestration of approximately 50% of absorbed dose, and is intended for long-term use. Therefore on the available data, the possibility cannot be excluded that for this medicine, patients changed from the innovator to the generic 70 mg weekly alendronate dose may subsequently have, on average, 10% greater exposure."

That is, the possibility of long term increased exposure (with attendant risks) is not excluded (or testable) by this one study.

Overall, the clinical evaluator recommended rejection due to unresolved safety issues notwithstanding the formal demonstration of bioequivalence.

Bioequivalence was tightly established for the alendronic acid 70 mg tablet based on the results of study 282-07. This transcended the apparent difference in dissolution performance, as noted by the clinical evaluator in the file note that was prepared after the applicant's response to the clinical evaluation report.

Issues:

1. There is no suggestion that there is an employee permanently in Australia with pharmaceutical qualification or regulatory experience. Answers during the course of the application have come from India or New Zealand. This would have to be remedied once Accord Healthcare Pty Ltd has achieved registration of any medicinal product.

2. This application demonstrates that the establishment of bioequivalence might not be sufficient *per se* to secure registration of a new generic. The application has demonstrated that Accord Healthcare Pty Ltd's generics are of suitable quality. The product information document and the CMI are close to resolution. However, the 70 mg strengths are not really interchangeable by reason of differential size and the impossibility of crushing or dividing the generic of innovator tablet. Post-marketing experience with the innovator has determined the need for special attention to swallowing the tablet which requires taking a full glass of water and remaining in the upright position. A larger tablet may pose greater risks and the clinical evaluator has canvassed this. The Delegate was unaware of post-marketing data and of any consumer acceptance testing of the proposed 70 mg tablet, noting that crushing or dividing this tablet is not an option. The tablets are uncoated; this aspect provides less margin of safety if there is a somewhat prolonged residence/transit time in the oesophagus.

3. The 10 mg tablet presents fewer problems apart from relying on the demonstration of bioequivalence of the 70 mg tablets to support indirect bioequivalence of the respective 10mg tablets. This reliance depends on the advisory committee's answer to Question 1 below.

The Delegate considered that the application should be rejected due to unacceptable presentation of the 70 mg tablet, particularly in regard to potential safety concerns, and due to inadequate bioequivalence data for the 10 mg tablet.

Questions asked of ACPM:

1. Is the statistically significantly greater absorption of alendronic acid from Accord Healthcare Pty Ltd's alendronic acid 70 mg tablet of sufficient concern with regard to potentially greater long term absorption to require a clinical equivalence and safety study as a precondition for registration?

2. Notwithstanding the answer to Question 1, is the large tablet size for an ulcerogenic drug like alendronate enough to require further pre-market study (for example, in a clinical equivalence and safety study, to include endoscopic monitoring) or targeted postmarketing surveillance?

3. Can the 10 mg tablet be registered on the basis of indirect comparison via the 70mg tablets?

Response by the Sponsor

The sponsor responded to the two questions asked of the ACPM. The sponsor indicated that its alendronate sodium 70 mg has been approved by 17 countries of Europe (including UK and Sweden) through the decentralized procedure (with UK as the Reference Member State) and has been marketed since August 2008 in Europe.

Hence, the product has undergone extensive independent evaluation by 17 European agencies. The same difference in the size of the tablet exists between Accord's product and the European innovator as it exists between Accord's product and Australian innovator. However, this difference was not considered significant by any of the European agencies and the issue was not raised during evaluation.

Accord's product has been marketed in 4 countries (Germany, UK, Italy, The Netherlands) of Europe since August 2008 and the evidence from the post marketing data does not show any specific size related reports of oesophageal effects. Hence, the actual data from the market substantiates the fact that the size of the tablet may not pose any additional threats to the safety.

The Consumer Medicine Information (CMI) for the product contains a "When and How to take tablets" section, in line with that of the innovator, where explicit instructions have been provided for care to be taken while taking the product, so that any incidences of upper GI track irritation can be avoided.

The sponsor agreed that the overall extent of alendronate excretion was found to be higher for the test formulation by approximately 10% when compared to the reference product, so the 90% CI of test/reference ratio lay above unity.

In order to find out the route cause for obtaining higher extent of excretion, clinical, bio-analytical and pharmacokinetic/statistical data of this study were reviewed. However, there was no abnormal observation/ anomaly observed during the conduct of the study which could be attributed to higher extent of excretion.

It was noted that alendronate possesses a very high intra and inter subject variation in pharmacokinetics which is evident in the published literature and the result of present replicate designed study. The highly variable nature of alendronate could have attributed to the observed higher excretion rate with test formulation.

Apart from this, it was noted that although the extent of excretion for test formulation is observed to be on the higher side compared to the reference product in the present study; total amount of excreted alendronate with test profile ($AURC_{\infty}$: 236.312 mL*mcg/mL) is comparable with that of reported literature (Ae_{∞}: 237.2 mcg).

Moreover, according to the TGA-adopted EU guideline,[1] the test product can be concluded to be bioequivalent to the reference product if the 90% CI for primary parameters (R_{max}, $AURC_{last}$ and $AURC_{\infty}$ as set in the protocol) fall within the acceptance range of 80-125%. There is no specified criterion in the guideline that 90% CI should span unity.

The EU definition of bioequivalence states that two medicinal products are bioequivalent if their bioavailabilities are similar to such a degree that their effects will be essentially the same. It was noted that there is no requirement in this definition that the bioavailabilities of the test and reference product be identical.

These long-standing and internationally agreed acceptance criteria for bioequivalence studies were based on a clinical decision that, for most drugs, a change of ±20% would not be clinically significant. Therefore, two products can be considered bioequivalent if there is a 90% chance that their bioavailabilities do not differ by more than 20%. That is, the 90% CI lies within the acceptable range. As long as the relative bioavailabilities fall within this range, no matter where within this range, the products can be concluded to be bioequivalent; thereby not requiring the confidence interval to span unity.

In this study, the 90% confidence interval of all the three primary parameters fell within the acceptance range of 80-125% and therefore the test and reference products can be concluded to be bioequivalent.

Advisory Committee Recommendation

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended the registration of the 10 mg tablets for the indication:

For the treatment of osteoporosis.*

** Prior to treatment, osteoporosis must be confirmed by:*

the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults; or by

the presence of osteoporotic fracture.

For the treatment and prevention of glucocorticoid-induced osteoporosis in postmenopausal women not receiving oestrogen and who are on long-term corticosteroid therapy.

A specific pre-condition of approval should be applied that the Delegate is satisfied that the sponsor has the commitment, capacity and capability to deliver the required PSUR reports and to the engagement of appropriate, qualified persons that have responsibility for pharmacovigilance of the registered goods and are able to provide the TGA with PSUR reports at the required periods.

ACPM recommended rejection of the submission to register the 70 mg tablets.

In making this recommendation, the ACPM advised that there were significant safety issues associated with the ingestion of a large, uncoated alendronate tablet by the predominantly ageing target population and as the data were based on studies predominantly in a young male cohort this did not provide sufficient evidence to support approval. The ACPM advised that adequate evidence might be generated by specific clinical studies or from postmarketing data.

Initial Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Alendraccord, Alendrocor and Pharmacor Alendronate containing 10 mg alendronic acid with the indications:

for the treatment of osteoporosis.*

for treatment and prevention of glucocorticoid-induced osteoporosis in post menopausal women not receiving oestrogen and who are on long term corticosteroid therapy.

**Prior to treatment, osteoporosis must be confirmed by the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults or by the presence of osteoporotic fracture.*

TGA rejected that part of the submission to register Alendraccord, Alendrocor and Pharmacor Alendronate containing 70 mg alendronic acid.

A further specific condition applicable to these therapeutic goods is that the sponsor must have engaged suitable qualified persons, residing in Australia, that have responsibility for pharmacovigilance of the registered goods and are able to provide the TGA with PSUR reports at the required periods.

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Delegate of the Minister reviewed the data submitted in the submission prepared by the sponsor which accompanied its letter seeking a review of the initial decision.

The Delegate of the Minister noted that the 10 mg and 40 mg forms of the innovator brand of alendronate sodium tablets were recommended for approval for marketing in Australia by the Australian Drug Evaluation Committee (which preceded the ACPM) in February 1996. The products had already been available in some other countries. By October 1996, reports had been published illustrating that alendronate can cause chemical oesophagitis, including severe ulcerations, in some patients.[2] Alendronate belongs to the bisphosphonate class of medicines. In an editorial in 2000, David Y Graham MD, Veterans Affairs Medical Centre, Houston, Texas stated that "The clinical data support the notion that gastrointestinal damage associated with bisphosphonate therapy is a formulation problem and that reformulation should reduce or eliminate both oesophageal and gastric damage. One presumes that clever individuals within the pharmaceutical industry could devise a method that would prevent the high local concentrations of the drug and/or decrease the probability that the tablet would remain in the oesophagus while maintaining the bisphosphonate as a bioavailable and effective medication."[3] The same author went on to add that "Bisphosphonates are very useful drugs and one can predict that their use will continue and grow. Until there is an oesophageal-safe bisphosphonate, the use of these drugs can be considered to be a form of oesophageal roulette. Additional studies are needed and reformulation should be considered to eliminate the possibility of the development of high local concentrations of these drugs in the oesophagus or stomach."

The Delegate of the Minister further noted that alendronate sodium 70 mg tablet proposed for marketing in Australia by the sponsor was significantly larger in terms of length, width and thickness than the innovator product (Fosamax). The differences are clearly set out in Table 3. The sponsor's candidate tablet was 4.5 mm longer, almost 2 mm wider and 1.8 mm thicker than the registered Fosamax 70 mg tablet. The extra dimensions were also reflected in the tablet weight. The sponsor's tablet was stated to weigh 770 mg which was more than double the weight of the Fosamax 70 mg tablet. The Delegate of the Minister noted the opinion of the expert Australian advisory committee (ACPM) which, in its recommendation to reject the submission for registration of the product, stated that "there were significant safety issues

[2] See, for example, De Groen P, Lubbe D, Hirsch L et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996; 335: 1016-21.

[3] Graham DY. Bisphosphonate gastrointestinal damage: perspective and research needs. Pharmacoepidemiol Drug Safety 2000; 9: 377-381.

associated with the ingestion of a large, uncoated alendronate tablet by a predominately ageing target population."

The Delegate of the Minister noted that in the sponsor's letter of appeal, it was stated that "Accord Healthcare contends that there is no actual evidence or data supporting the view that the proposed larger tablets would enhance the potential of oesophageal adverse events. On the contrary there is sufficient evidence from the post-marketing data available to the sponsor from a large patient population, which establishes the safety of the proposed tablets"

and

"There have been 150 case reports, out of which 106 were regulatory reports, 41 were derived from the scientific literature and 3 reported directly to the company. Out of the 150 case reports there are none for which the size of the tablet has been attributed as a cause of the adverse event."

The Delegate of the Minister reviewed the information submitted by the sponsor in its appeal with reference to a "Review of Post-Marketing Data for Alendronic Acid" (hereafter referred to as The Review). It was said to be based on Accord Healthcare's global safety database with a cut-off (data lock point) of 31 October 2010. It was stated that the Accord alendronic acid 70 mg tablets have been marketed in European countries since June 2009, commencing in the United Kingdom and Netherlands. The report indicated that as at the cut-off date the product was marketed in seven European countries. It calculated a total patient exposure based on sales and an assumption of duration of use.

The Review stated that the global safety database includes details of 150 case reports, of which 33 can be excluded from implicating the Accord product as the date of the adverse event was before the product was marketed. There was also reference to 15 reports identifying the suspect product as Fosamax. In order for the arithmetical calculation to be correct (150 minus 33=117), the Fosamax reports must have also been included in the 33 reports submitted prior to the Accord product's launch.

It was submitted that there were 117 reports in which, although none of the reports mention Accord alendronate as the suspect drug, Accord alendronate 70 mg cannot be excluded as a suspect drug. The Delegate of the Minister noted however that it was also stated that three adverse event reports, seemingly included in the 117 reports, were submitted directly to the company (one in UK; two in Netherlands) and at least one of those reports specifically implicated the Accord product (UK report).

The Review identified that 75 of the cases included mention of adverse events falling within the MedDRA System Organ Classes "Gastrointestinal disorders" (40 cases), "General disorders" (21 cases), "Neoplasms" (4 cases) and "Respiratory Disorders" (10 cases).

The Review noted that 15 Preferred Terms (presumably falling within the four above-mentioned System Organ Classes) were included in the United Kingdom Summary of Product Characteristics. No further information was provided about those reports.

The Review also noted that the cases included mention of eight Preferred Terms which were not mentioned in the United Kingdom Summary of Product Characteristics. Based on the dates of occurrence or the name of the suspect drug, the Accord 70 mg product may be excluded as a cause of haematochezia, from one of two reports of chest discomfort, from the two reports of oesophageal adenocarcinoma, from a case of pharyngeal cancer stage unspecified and from one of two cases of chest tightness. There thus remained three reports of haematemesis, one report of chest discomfort, three reports of chest pain and one report of

oesophageal carcinoma in respect of which it is possible that the Accord 70 mg product played a causal role.

The Delegate of the Minister noted that the reporting directly to the sponsor included a report by a consumer in the United Kingdom that mentioned that the patient had experienced heartburn/digestive discomfort which the patient considered was attributable to the size of the Accord alendronic acid 70 mg tablet. The Review follows the current European approach to pharmacovigilance by commenting that "the case lacked adequately medically confirmed information".

The Delegate of the Minister also noted that, since 31 October 2010, the sponsor has become aware of a report obtained via the Dutch drug safety monitoring organisation Lareb, discussing "nightly substernal pain" in a patient after switching treatment from Fosamax to the Accord 70 mg tablets. It was stated that the physician was unsure whether the events were related to the Accord product. It was claimed that "in the presence of a positive de-challenge, the causal role of the Accord product could not be ruled out".

Concerning this Review, the Delegate of the Minister made the following observations:

- The calculations in the Review concerning estimated numbers of persons exposed to the Accord 70 mg product appear to be based on sales (ex company) figures. There was no allowance for stock still in the supply chain, which would reduce the estimated number exposed. No data on the actual numbers of packs dispensed were provided.
- The submitted information related to spontaneous reporting of suspected adverse reactions, either to national monitoring centres and regulatory agencies or to the marketing company and its representatives in the seven countries. Under-reporting is known to occur with spontaneous reporting. Under- reporting is documented to be more common after a new medicine has been on the market for about two or more years. This phenomenon is sometimes called the Weber Effect. It presumably occurs because healthcare professionals have become aware of a particular medicine-adverse effect association, regard it as already well-known and are thus not motivated to report it. Oesophageal damage, manifest by a variety of symptoms, has been well-documented and widely-known with alendronate tablets for more than a decade. It may thus be reasonably expected that by the time that the Accord 70 mg product entered the European market, under-reporting of adverse oesophageal effects of alendronate had become very common and underlies the overall low reporting.
- For a healthcare professional to attribute and to be motivated to report an adverse effect to a particular generic product requires that person to know the identity of the product. In Australia, pharmacists may choose which of several generic versions of a product to dispense, and this may vary from time to time at an individual pharmacy. A consequence of this is that those doctors or other healthcare professionals who are informed of a possible adverse effect of a medicine by a patient may have no idea of the actual product involved. In its defence of its product in the Review, the sponsor has not given any consideration as to whether the treating healthcare professionals in the seven countries would indeed know that the patient had taken the Accord 70 mg product.
- The pharmacovigilance system in Australia has long had a policy of accepting, assessing and recording reports from patients and other consumers. The possible importance of individual reports from patients and other consumers is not downgraded by such considerations as "lacked adequate medically confirmed information" as happens in Europe. With that in mind, a careful consideration of the information in the review discloses that:

- prior to 31 October 2010 there was a report in the United Kingdom of a patient who attributed heartburn and digestive discomfort to the size of the Accord alendronate 70 mg tablet.
- that since 31 October 2010, there has been a report to Lareb in the Netherlands in which the patient specifically attributed nightly substernal pain to a switch from Fosamax to Accord alendronic acid 70 mg tablets. Presumably because the patient recovered after ceasing the Accord product, the Review states that there had been a positive de-challenge. In Australia, that would raise the possibility that the appropriate causality assessment should be that the Accord product was a probable cause, in contrast to the "could not be ruled out" stated in the Review. Further, if there was "nightly" substernal pain, there is a real possibility that the patient was experiencing discrete positive rechallenges each night, in which case the Australian causality grading would be "certain".

In the view of the Delegate of the Minister, these reports do support the possibility that needs further exploration that the large tablet size of the Accord 70 mg alendronic acid tablet is associated with an increased risk of damage to the oesophagus.

The Delegate of the Minister noted that it was proposed that the sponsor will "introduce a scoreline on the 70 mg tablets", making it possible for users to break the tablet into two halves and "make swallowing of the tablet easier." The sponsor has proposed to include in the Product Information and Consumer Medicines Information the words *"the scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablet can be divided into two halves."* The Delegate of the Minister was not satisfied that the proposal was an adequate solution to the risk posed by the product's large tablet size. Even if wording were included on the packaging in addition to wording in the Product Information and Consumer Medicines Information, there can be no confidence that there will be complete compliance with the advice. This is particularly so when a high proportion of those who would be taking the product are elderly, including those elderly subjects who are dependent on carers for the appropriate administration of their medicines.

The Delegate of the Minister decided to confirm the initial decision to refuse registration.

The reasons for the decision were:

- Published literature confirms that alendronate taken by mouth may be associated with severe oesophageal and gastric damage, such as ulceration;
- The large tablet size may be expected to increase the possibility that a tablet may pass more slowly through or lodge in the oesophagus. There can be no certainty that instructions to patients to take measures to avoid such events will be followed or, if followed, will be effective in preventing slow passage or lodging in the oesophagus.
- The combination of the drug's potential to cause severe oesophageal and gastric damage and the significantly larger tablet size of the product compared with the reference product caused the Delegate of the Minister not to be satisfied as to the safety of the product, which is a requirement of s25 of the Act;
- The Delegate of the Minister noted the advice of the ACPM that there are significant safety issues associated with the ingestion of a large, uncoated alendronate tablet by a predominately ageing target population. The Delegate of the Minister agreed with that advice, which further causes the Delegate of the Minister not to be satisfied as to the safety of the product, which is a requirement of s25 of the Act;

- The Delegate of the Minister noted that the ACPM advised that adequate evidence to support the approval of the tablet as a safe product in Australia might be generated by specific clinical studies or from post-marketing data. The appeal documentation did not include any new safety information derived from specific clinical studies. The Delegate of the Minister considered the sponsor's Review of Post-Marketing Data for Alendronic Acid.
  In the view of the Delegate of the Minister, the extent of exposure may have been overstated. Further, there are strong reasons for believing that reporting of suspected adverse reactions to generic versions of medicines may be considerably less than with the innovator product. For these reasons, the submitted information did not cause the Delegate of the Minister to change his view that he was not satisfied that the product is safe. To the contrary, the Delegate of the Minister noted that two reports in Europe have attributed symptoms of gastrointestinal adverse events to the large size of the sponsor's product. That information reinforces the view of the Delegate of the Minister that he was not satisfied that the product is safe.
- The Delegate of the Minister considered the sponsor's proposal to incorporate a scoreline into the tablet. He was not satisfied that this proposal is an adequate solution to the risk posed by the product's large tablet size, as there is likely to be inadequate compliance with instructions about how to take the two half tablets.

For these reasons, the Delegate of the Minister decided to confirm the initial decision made by the Delegate of the Secretary because he was not satisfied that Accord Healthcare Pty Ltd has established that the product is safe for the purposes for which it is to be used.

The Delegate of the Minister took the opportunity to advise the sponsor that he accepted the advice of the ACPM that it did not include the observed small increase in bioavailability as a reason for rejection of this application.

The Delegate of the Minister also took the opportunity to advise the sponsor of a related matter which did not form part of the reasons for the decision. At his request, the Office of Laboratories and Scientific Services of the TGA sampled four generic alendronate sodium 70 mg tablets currently registered and supplied in Australia. Those products may each also be marketed under other product names. Two of the sampled products are round tablets with dimensions of 10.10 mm and 11.10 mm respectively. The other two (oblong) tablets have dimensions that at most exceed the length of a Fosamax tablet by 0.17 mm, at most exceed the width of a Fosamax tablet by 0.80 mm and at most exceed the thickness of a Fosamax tablet by 0.01 mm.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Alendraccord Tablets 10 mg

(Alendronate Sodium Tablets 10mg)

NAME OF THE MEDICINE

Alendronate Sodium

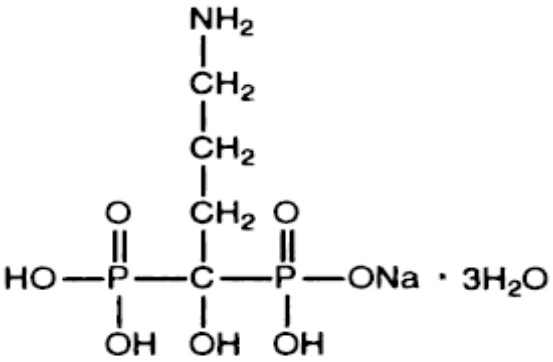
Chemical name: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

Molecular formula: $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$,

The molecular weight is 325.12

CAS Registry Number is: 121268-17-5

The structural formula is



DESCRIPTION

Alendronate sodium, is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Alendraccord Tablets (Alendronate Sodium) are available as 10mg oral uncoated tablets. Each tablet of Alendraccord contains 13.05 mg of alendronate sodium, which is the molar equivalent to 10 mg of alendronic acid. In addition to the active ingredient alendronate sodium, each Alendraccord tablet contains the following

inactive ingredients: Cellulose-microcrystalline, lactose anhydrous, croscarmellose sodium and magnesium stearate.

PHARMACOLOGY

PHARMACOKINETIC PROPERTIES

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. There was substantial variability both within and between patients, coefficient of variation 63% and 77%, respectively. Oral bioavailability in men (0.6%) was similar to that in women.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis studies, Alendronate Sodium Tablets were effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In normal subjects, oral prednisone (20 mg three times daily for five days) did not substantially alter the oral bioavailability of alendronate (alendronate alone, 0.73%; alendronate plus prednisone, 0.87%).

Distribution

Preclinical studies show that alendronate transiently distributes to soft tissues following administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of alendronate in plasma following therapeutic oral doses are generally below the limits of quantification (less than 5 ng/mL). Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolised in animals or humans.

Elimination

Following a single 10 mg IV dose of [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces; the renal clearance of alendronate was 71 mL/min.

Plasma concentrations fell by more than 95% within 6 hours following IV administration, due to distribution to the bone and excretion in the urine. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicines by those systems in humans.

Preclinical studies show that the alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found over three weeks in rats, with a cumulative IV dose of 35 mg/kg. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Bioavailability

Alendraccord 10mg tablets have been registered on the basis that they are a direct scale of a 70mg test tablet containing alendronate 70mg that has been shown to be bioequivalent to Australian-sourced Fosamax 70mg tablets in a large conventional bioequivalence study. The study was an open label, balanced, randomised, single dose, two-treatment, four period, replicate, two-sequence, two-way crossover oral bioequivalence study of alendronate sodium tablets, 70 mg (test product, B) in comparison with Fosamax® 70 mg (reference product, A) in 120 healthy adult men under fasting conditions. This study measured urinary alendronate excretion. Based on urinary excretion of alendronate, the following comparisons and statistical analyses were made:

Parameters(units)	ln-transformed Geometric Least Squares Mean			90% Confidence intervals (parametric)	Intra-subject CV (%)
	Test Product alendronate 70mg (B)	Reference Product Fosamax 70mg (A)	Ratio (B/A) %		
Max_rate (mL*ng/mL/h)	73003.869	70239.278	103.9	96.81-111.59	A 50.8 B 39.9
AURC_last (mL*ng/mL)	207129.392	187308.128	110.6	102.42-119.39	A 47.5 B 43.8
AURC_INF (mL*ng/mL)	213949.772	193042.704	110.8	102.77-119.53	A 47.9 B 43.2

The 90% CI fell within the acceptance limits of 80-125% required for bioequivalence as set out in the protocol, for all three pre-specified parameters, Max_rate (mL*ng/mL/h); AURC_last (mL*ng/mL) and AURC_INF (mL*ng/mL). Bioequivalence was therefore established.

PHARMACODYNAMIC PROPERTIES

Alendronate is a bisphosphonate that, in animal studies, localises preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass (see Clinical Trials section for details). Following exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

The relative inhibitory activities on bone resorption and mineralisation of alendronate and etidronate were compared in growing rats. The lowest dose of alendronate that

interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding safety margin for etidronate was one to one. These data indicate that, unlike etidronate, alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

OSTEOPOROSIS

WHO utilises the definition of osteoporosis as a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. The diagnosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the gender specific mean for young adults) or by the presence or history of osteoporotic fracture. It occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Daily oral doses of alendronate in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following the discontinuation of alendronate despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with Alendronate Sodium Tablets 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with Alendronate Sodium Tablets. In osteoporosis treatment studies Alendronate Sodium Tablets 10 mg/day decreased the markers of bone formation, osteocalcin and total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months.

OSTEOPOROSIS IN MEN

Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. All men with osteoporosis should be investigated for hypogonadism and, if necessary, treated for this condition. Treatment of men with osteoporosis with Alendronate Sodium Tablets 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%.

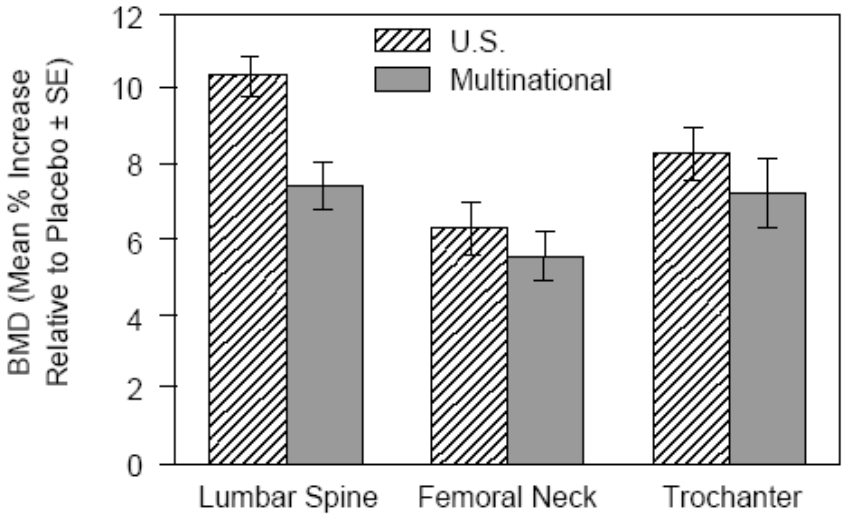
CLINICAL TRIALS

Postmenopausal women

Effect on bone mineral density

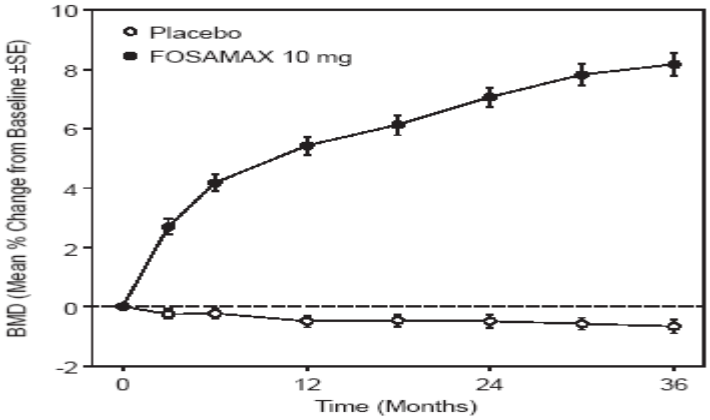
The efficacy of Alendronate Sodium Tablets 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in two large three year multicentre studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck and trochanter in patients receiving Alendronate Sodium Tablets 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Fig-1:-Increase in BMD
Alendronate Sodium Tablets 10 mg/day in Two Studies at Three Years



These increases were highly significant relative both to baseline and placebo at each measurement site in each study. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment (see figure below for lumbar spine results). In the two-year extension of these studies, treatment with Alendronate Sodium Tablets 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine 0.94%; trochanter 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, Alendronate Sodium Tablets appears to reverse the progression of osteoporosis as assessed by increased bone mineral density. Alendronate Sodium Tablets were similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use of concomitant medications.

Fig -2: Time Course of Effect of Alendronate Sodium Tablets 10 mg/day versus Placebo: Lumbar Spine BMD Percent Change from Baseline



In patients with postmenopausal osteoporosis treated with Alendronate Sodium Tablets 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those in the placebo groups. These data indicate that continuous treatment with Alendronate Sodium Tablets is required to produce progressive increases in bone mass.

The therapeutic equivalence of Alendronate Sodium Tablets once weekly 70 mg (n = 519) and Alendronate Sodium Tablets 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the70 mg once weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group.
The two treatment groups were also similar with regard to BMD increases at other skeletal sites. While there are no placebo-controlled fracture data for the once weekly 70 mg tablet, the increases in bone density support the expectation that Alendronate Sodium Tablets once weekly 70 mg will have effects to reduce the incidence of fractures similar to those of the 10 mg daily treatment (see below). The study was not designed to evaluate the relative compliance of Alendronate Sodium Tablets once weekly 70 mg and 10 mg daily.

Effect on fracture incidence

Although the US and Multinational studies (see above) were not designed to assess fracture rates as the primary endpoint, preplanned analysis of the data pooled across once daily doses at three years revealed a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with Alendronate Sodium Tablets experiencing one or more vertebral fractures (3.2%) relative to those treated with placebo (6.2 %). Furthermore, of patients who sustained any vertebral fracture, those treated with Alendronate Sodium Tablets experienced less height loss (5.9 mm vs 23.3 mm) due to a reduction in both the number and severity of fractures.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline vertebral

(compression) fracture and the Four-Year Study of patients with low bone mass but without baseline vertebral fracture.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline vertebral fracture)

This randomised, double-blind, placebo-controlled 2027-patient study, (Alendronate Sodium Tablets n=1022; placebo, n=1005) demonstrated that treatment with Alendronate Sodium Tablets resulted in clinically significant reductions in fracture incidence at three years as shown in the table -1. Data also showed statistically significant reductions in painful vertebral fractures and clinical fractures at other sites. Similar reductions of hip and wrist fractures were seen in five pooled osteoporosis treatment studies of two or three years duration.

Table-1

Effect of Alendronate Tablets on fracture incidence in the three-year study of FIT (% of patients with vertebral fracture at baseline)					
	Alendronate Tablets n = 1022	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %	P Value
Patients with:					
≥ 1 new vertebral fracture	7.9	15.0	7.1	47	<.001*
≥ 2 new vertebral fractures	0.5	4.9	4.4	90	<.001*
≥ 1 painful vertebral fracture	2.3	5.0	2.7	54	<.002**
Any painful (inc. vertebral) fracture	13.8	18.1	4.3	26	0.007**
Hip fractures	1.1	2.2	1.1	51	0.047**
Wrist (forearm) fractures	2.2	4.1	1.9	48	0.013**
* Mantel-Haenzel chi^2				**Log Rank test	

Furthermore, in this population of patients with baseline vertebral fracture, treatment with Alendronate Sodium Tablets significantly reduced the incidence of hospitalisations resulting from any cause (25.0%vs. 30.7%, a 20% relative risk reduction). This difference appears to be related, at least in part, to the reduction in fracture incidence.

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline vertebral fracture)

This randomised, double-blind, placebo-controlled, 4432-patient study (Alendronate Sodium Tablets, n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to Alendronate Sodium Tablets. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table-2 for the patients with osteoporosis.

Table -2

Effect of Alendronate Tablets on fracture incidence in Osteoporotic† Patients in the four-year study of FIT (patients without vertebral fracture at baseline)				
	% of Patients			
	Alendronate Tablets n = 1545	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
≥ 1 painful fracture	12.9	16.2	3.3	22**
≥ 1 vertebral fracture††	2.5	4.8	2.3	48***
≥ 1 painful vertebral fracture	1.0	1.6	0.6	(NS)
Hip fracture	1.0	1.4	0.4	(NS)
Wrist (forearm) fracture	3.9	3.8	-0.1	None

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fracture: Alendronate Sodium Tablets, n=1426; placebo, n=1428
ns Not significant. This study was not powered to detect differences at these sites.
**p = 0.01, ***p <0.001

Consistency of fracture results

The reductions in the incidence of vertebral fractures (Alendronate Sodium Tablets vs. placebo) in the Three and Four-Year Studies of FIT were consistent with that in the combined US and Multinational (US/Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with Alendronate Sodium Tablets reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (Three-Year FIT: 47% reduction, p<0.001; Four-Year FIT: 44% reduction, p=0.001 US/Mult, 48% reduction, p=0.034). In addition, Alendronate Sodium Tablets reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the US/Mult and Three-Year FIT studies (p<0.001). Thus, Alendronate Sodium Tablets reduced the incidence of vertebral fractures whether or not patients had experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of Alendronate Sodium Tablets in reducing the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with greatest morbidity.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with Alendronate Sodium Tablets at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralisation and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in ovariectomised rats and baboons exposed to long term alendronate treatment, indicate that bone formed during therapy with Alendronate Sodium Tablets is of normal quality.

Concomitant Use with Oestrogen/Hormone Replacement Therapy

The effects on BMD of treatment with Alendronate Sodium Tablets 10 mg once daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomised postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or Alendronate Sodium Tablets alone (both 6.0%).

The effects on BMD when Alendronate Sodium Tablets were added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of Alendronate Sodium Tablets 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Men

The efficacy of Alendronate Sodium Tablets 10 mg once daily in men with osteoporosis was demonstrated in a two-year, double-blind, placebo-controlled, multicentre study, which enrolled 241 osteoporotic men between the ages of 31 and 87 years. All patients in the study (97.5% of whom were Caucasian) had either:1) a BMD T-score $\leq$ -2 at the femoral neck and $\leq$ -1 at the lumbar spine or 2) a baseline osteoporotic fracture and a BMD T-score of $\leq$ -1 at the femoral neck. At two years the mean increases relative to placebo in BMD in men receiving Alendronate Sodium Tablets 10 mg daily were; lumbar spine 5.3%; femoral neck 2.6%; trochanter 3.1%; and total body 1.6% (all $p \leq 0.001$). Alendronate Sodium Tablets were effective regardless of age, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with the much larger studies in postmenopausal women, in these men Alendronate Sodium Tablets 10 mg daily reduced the incidence of new vertebral fracture (post-hoc analysis; assessment by quantitative radiography) relative to placebo (0.8% vs 7.1%, respectively; $p = 0.017$) and correspondingly, also reduced height loss (-0.6 vs –2.4 mm, respectively; $p = 0.022$).

The effects of discontinuation of Alendronate Sodium Tablets treatment have not been studied in this population.

Glucocorticoid - Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip and rib). It occurs both in males and females of all ages. Bone loss occurs as a result of a lower rate of bone formation relative to that of bone resorption. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of one year's duration, Alendronate Sodium Tablets 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bonespecific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 25 to 30% and 12 to 15%, respectively. As a result of inhibition of bone resorption, Alendronate Sodium Tablets 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1%) and serum phosphate (approximately 2 to 7%).

The efficacy of Alendronate Sodium Tablets 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year placebo controlled, doubleblind, multicentre studies (n: total = 560, males = 176) of virtually identical design. Most of the patients were ambulant, caucasian and non-smokers. The study population included patients with rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, pemphigus, asthma, myositis, inflammatory bowel disease, giant cell arteritis, sarcoidosis, myasthenia gravis, chronic obstructive pulmonary disease and nephrotic syndrome. The range and duration of prior corticosteroid use in the studies was 0 to 538 months with a mean of 43.6 months and a median of 12 months. The range of prednisone dose at study commencement was 5 to 135 mg/day with a mean of 18.4 mg and a median of 10 mg daily. Fifty-seven percent of patients had osteopenia/osteoporosis at study commencement. Patients received supplemental calcium and vitamin D. At one year, the mean increases relative to placebo in BMD in patients receiving Alendronate Sodium Tablets 5 mg/day from the combined studies were: lumbar spine, 2.41%; femoral neck, 2.19%; and trochanter, 1.65%. These increases were significant at each site. Total body BMD was maintained with Alendronate Sodium Tablets 5 mg/day indicating that the increase in bone mass of the spine and hip did not occur at the expense of other sites. The increases in BMD with Alendronate Sodium Tablets 10 mg/day were similar to those with Alendronate Sodium Tablets 5 mg/day in all patients except for postmenopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with Alendronate Sodium Tablets 10 mg/day were greater than those with Alendronate Sodium Tablets 5 mg/day at the lumbar spine (4.11% vs. 1.56%) and trochanter (2.84% vs. 1.67%), but not at other sites. Alendronate Sodium Tablets were effective regardless of dose or duration of glucocorticoid use. In addition, Alendronate Sodium Tablets were similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received Alendronate Sodium Tablets at doses of up to 10 mg/day.

INDICATIONS

Indications for Alendraccord Tablets

Alendraccord Tablets 10mg are indicated for the treatment of:

- Osteoporosis*, including glucocorticoid- induced osteoporosis.

Alendraccord Tablets 10 mg are also indicated for prevention of

- Osteoporosis in post menopausal women with low bone mass (at least 1 standard deviation below the mean for young adults) not receiving oestrogen.
- Glucocorticoid- induced osteoporosis in those patients on long term corticosteroid therapy (see Clinical trials).

* Prior to treatment, osteoporosis must be confirmed by:

• the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults

or by

• the presence of osteoporotic fracture.

CONTRAINDICATIONS

- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcaemia (see PRECAUTIONS)

PRECAUTIONS

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE DOSAGE AND ADMINISTRATION. PHYSICIANS SHOULD THEREFORE BE ALERT TO ANY SIGNS OR SYMPTOMS SIGNALING A POSSIBLE OESOPHAGEAL REACTION. PATIENTS SHOULD BE INSTRUCTED TO DISCONTINUE ALENDRACCORD TABLETS AND SEEK MEDICAL ATTENTION IF THEY DEVELOP DYSPHAGIA, ODYNOPHAGIA OR RETROSTERNAL PAIN.

GENERAL

Causes of osteoporosis other than hypogonadism, aging and glucocorticoid use should be considered. If there are clinical reasons to suspect hypocalcaemia and/or vitamin D deficiency (serum levels 25 hydroxyvitamin D < 9 nmol/L), the appropriate diagnostic tests should be performed. Hypocalcaemia must be corrected before initiating therapy with Alendronate Sodium Tablets (See CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Alendronate Sodium Tablets.

Small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Alendronate, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalisation.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking Alendronate Sodium Tablets and/or who fail to swallow it with the recommended amount of water, and/or who continue to take Alendronate Sodium Tablets after developing symptoms suggestive of oesophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION).

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when Alendronate Sodium Tablets are given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis, or ulcers.

DENTAL

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates including Alendronate Sodium Tablets (see ADVERSE EFFECTS, *Post-Marketing Experience*). As of May 2004, ONJ after bisphosphonate treatment has been described in a total of 99 cases in two large case series, 7 of which were taking oral bisphosphonates. As of 3 Nov 2006, the Australian Adverse Drug Reactions Advisory Committee has received 25 reports of ONJ in patients receiving alendronate. Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection) and smoking.

Prior to treatment with bisphosphonates, a dental examination with appropriate preventative dentistry should be considered in patients with possible risk factors.

Before commencing invasive dental procedures, patients and their dentist should be advised of the risks and reports of osteonecrosis of the jaw so that dental symptoms, including toothache, developing during treatment can be fully assessed for cause before treatment of the tooth commences.

For patients requiring invasive dental surgery (eg. tooth extraction, dental implants), there are no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Therefore clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including discontinuation of bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

In patients who develop ONJ while on bisphosphonate therapy, the clinical judgment of the treating physician should guide the management plan to include appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be based on individual benefit/risk assessment. Surgery at the affected area may exacerbate the condition.

ATYPICAL STRESS FRACTURES

A small number of long-term (usually longer than three years) alendronate-treated patients developed stress fractures of the proximal femoral shaft (also known as insufficiency fractures). Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reported cases of this condition is very low (some 40 reported cases world-wide). Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on individual benefit/risk assessment. A cause and effect relationship between bisphosphonate use and stress fractures has not been excluded.

MUSCULOSKELETAL PAIN

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see ADVERSE EFFECTS, *Post-Marketing Experience*). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

RENAL INSUFFICIENCY

Alendraccord Tablets are not recommended for patients with creatinine clearance < 35mL/min (see DOSAGE AND ADMINISTRATION).

DOSING INSTRUCTIONS FOR PATIENTS

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow each tablet of Alendraccord Tablets with a full glass of water. Patients should be instructed not to lie down for at least 30

minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take Alendraccord Tablets at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. Patients should be instructed that if they develop symptoms of oesophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking Alendraccord Tablets and consult their physician.

EFFECTS ON FERTILITY

Alendronate sodium had no effect on fertility in male and female rats at oral doses of up to 9 and 15 mg/kg/day.

USE IN PREGNANCY (Category B3)

Alendronate has not been studied in pregnant women and should not be given to them. In studies with pregnant rats, oral alendronate doses of 2 mg/kg/day and above resulted in dystocia due to maternal hypocalcaemia. Foetal weight was reduced in rats at maternal doses greater than 5 mg/kg/day. No teratogenic effects were seen in rats or rabbits at oral doses up to 25 and 35 mg/kg/day, respectively.

Australian Categorization Definition of *Category B3 :-* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans

USE IN LACTATION

Alendraccord Tablets have not been studied in breastfeeding women and should not be given to them.

PAEDIATRIC USE

Alendraccord Tablets have not been studied in children and should not be given to them.

USE IN THE ELDERLY

In controlled trials, there was no age-related difference in the efficacy or safety profiles of Alendronate Sodium Tablets.

CARCINOGENICITY

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

GENOTOXICITY

Alendronate did not cause gene mutations in bacteria or in mammalian cells *in vitro*, nor did it cause DNA damage in rat hepatocytes *in vitro* (alkaline elution assay). In assays of chromosomal damage, alendronate was weakly positive in an *in vitro* assay using Chinese hamster ovary cells at cytotoxic concentrations (≥5mM), but was negative at IV doses up to 25 mg/kg/day (75 mg/m^2) in an *in vivo* assay (chromosomal aberrations in mouse bone marrow).

INTERACTIONS WITH OTHER MEDICINES

If taken at the same time it is likely that calcium supplements, antacids and other oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking Alendraccord tablets before taking any other oral medication.

No other drug interactions of clinical significance are anticipated though the concomitant medication with two or more bisphosphonates cannot be recommended because of the lack of clinical data.

Concomitant use of HRT (oestrogen ± progestin) and Alendronate Sodium Tablets was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of Alendronate Sodium Tablets and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see ADVERSE EFFECTS), Clinical Studies, Concomitant use with oestrogen/hormone replacement therapy).

Specific interaction studies were not performed. Alendronate Sodium Tablets (10 mg and 5 mg/day) were used in studies of treatment and prevention of osteoporosis in postmenopausal women, men and glucocorticoid users, with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions. In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of Alendronate Sodium Tablets greater than 10 mg and aspirin-containing products.

Since Non Steroidal Anti-inflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

EFFECT ON ABILITY TO DRIVE OR USE MACHINERY

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with

alendronate sodium tablets may affect some patients' ability to drive or operate machinery.
Individual responses to Alendronate Sodium Tablets may vary (see ADVERSE EFFECTS).

EFFECT ON LABORATORY TESTS

In double-blind, multicentre, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking Alendronate Sodium Tablets versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P/dL (0.65 mM) were similar in both treatment groups.

ADVERSE EFFECTS

CLINICAL STUDIES
In clinical studies Alendronate Sodium Tablets were generally well tolerated. In studies of up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

Treatment of osteoporosis
Postmenopausal women

Alendronate Sodium Tablets have been evaluated for safety in clinical studies in approximately 5000 postmenopausal patients. In two three-year, placebo controlled, double blind multicentre studies, discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with Alendronate Sodium Tablets 10 mg/day and 6.0% of 397 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either Alendronate Sodium Tablets 10 mg/day or placebo are presented in the following table-3

Table-3

Drug Related Adverse Experiences Reported in ≥1% of Patients		
	Alendronate Sodium 10mg/day % (n=196)	PLACEBO % (n=397)
Gastrointestinal		
abdominal pain	6.6	4.8
Nausea	3.6	4.0
Dyspepsia	3.6	3.5
Diarrhoea	3.1	1.8
constipation	3.1	1.8
Flatulence	2.6	0.5
acid regurgitation	2.0	4.3
oesophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distension	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

Rarely, rash and erythema have occurred.

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of Alendronate Sodium Tablets 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued Alendronate Sodium Tablets 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with Alendronate Sodium Tablets 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: Alendronate Sodium Tablets, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with Alendronate Sodium Tablets 5 or 10 mg/day.

In a one-year, double-blind, multicentre study, the overall safety and tolerability profiles of Alendronate Sodium Tablets once weekly 70 mg (n = 519) and Alendronate Sodium Tablets 10 mg daily (n = 370) were similar. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in≥1% of patients treated with either patient group are presented in the following table-4

Table-4

Drug Related Adverse Experiences Reported in ≥ 1% of Patients		
	Alendronate Tablets 70mg/day % (n = 519)	Alendronate Tablets 10mg/day % (n = 370)
Gastrointestinal		
Abdominal pain	3.7	3.0
Dyspepsia	2.7	2.2
Acid regurgitation	1.9	2.4
Nausea	1.9	2.4
Abdominal distension	1.0	1.4
Constipation	0.8	1.6
Flatulence	0.4	1.6
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Concomitant use with oestrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with Alendronate Sodium Tablets 10 mg once daily and oestrogen ± progestin (n=354) was consistent with those of the individual treatments.

Men

In a two year, placebo-controlled, double-blind, multicentre study, the safety profile of Alendronate Sodium Tablets 10 mg daily in 146 men was generally similar to that seen in postmenopausal women.

Treatment and prevention of glucocorticoid - induced osteoporosis.

In two, one-year, placebo-controlled, double-blind, multicentre studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of Alendronate Sodium Tablets 5 and 10 mg/day were generally similar to that of placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in≥1% of patients treated with either Alendronate Sodium Tablets 5 mg/day, 10 mg/day or placebo are presented in the following table-5:

Table -5

Drug Related Adverse Experiences Reported in ≥ 1% of Patients			
	Alendronate Tablets 10mg/day	Alendronate Tablets 5mg/day	Placebo
	%	%	%
Gastrointestinal			
Abdominal pain	3.2	1.9	0.0
Acid regurgitation	2.5	1.9	1.3
Constipation	1.3	0.6	0.0
Melena	1.3	0.0	0.0
Nausea	0.6	1.2	0.6

Post-marketing Experience

The following adverse effects have been reported in post-marketing use with alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcaemia has occurred, generally in association with predisposing conditions. Rarely, peripheral oedema.

Gastrointestinal: nausea, vomiting, oesophagitis, oesophageal erosions, oesophageal ulcers, rarely oesophageal stricture or perforation, and oropharyngeal ulceration; rarely, gastric or duodenal ulcers, some severe and with complications (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), often with delayed healing, has been reported rarely.

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see PRECAUTIONS); joint swelling, atypical stress fracture (see PRECAUTIONS).

Nervous System: dizziness, vertigo, dysgeusia.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special senses: rarely uveitis; scleritis or episcleritis.

DOSAGE AND ADMINISTRATION

Alendraccord Tablets must be taken at least 30 minutes before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food and some medications are likely to reduce the absorption of alendronate (see INTERACTIONS WITH OTHER MEDICINES).

Alendraccord Tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, Alendraccord Tablets should only be swallowed with a full glass of water.

Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendraccord Tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experiences (see PRECAUTIONS).

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE PRECAUTIONS. PATIENTS SHOULD BE INSTRUCTED THAT IF THEY DEVELOP SYMPTOMS OF OESOPHAGEAL DISEASE (SUCH AS DIFFICULTY OR PAIN UPON SWALLOWING, RETROSTERNAL PAIN OR NEW OR WORSENING HEARTBURN) THEY SHOULD STOP TAKING ALENDRACCORD TABLETS AND CONSULT THEIR PHYSICIAN.

In clinical trials, Alendronate Sodium Tablets were administered with appropriate calcium and vitamin D supplementation. The use of vitamin D as the sole treatment of osteoporosis has not been established.

Patients should receive supplemental calcium and/or vitamin D, if intake is inadequate (see PRECAUTIONS). Physicians should consider the vitamin D intake from vitamins and dietary supplements. Additional supplements should not be taken at the same time of the day as Alendronate Sodium Tablets.

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendraccord tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min).

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to Alendronate Sodium Tablets, there are no known or theoretical safety concerns related to Alendronate Sodium Tablets in patients who previously received any other antiosteoporotic therapy.

<u>Treatment of osteoporosis</u>

The recommended dosage is:

• one 10 mg tablet of Alendraccord tablets once daily

<u>Treatment and prevention of glucocorticoid - induced osteoporosis</u>

For postmenopausal women not receiving oestrogen, the recommended dosage is one 10 mg tablet of Alendraccord tablets once a day (see Clinical Trials, Glucocorticoid - Induced Osteoporosis).

OVERDOSAGE

No specific information is available on the treatment of overdosage with alendronate. Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. Administration of milk or antacids, to bind alendronate, should be considered.

Contact the Poisons Information Centre (telephone 13 11 26) for advice regarding management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Alendraccord Tablets 10 mg (AUST R 161444): White to off white, oval, biconvex tablet debossed with “10” on one side and plain on other side.

Supplied in blister packs of 30 tablets.

STORAGE CONDITIONS
Store below 25°C.

Keep the pack in a dry place and store tablets in original blister package until use.

NAME AND ADDRESS OF THE SPONSOR

Accord Healthcare Pty Ltd

Unit 702/23 Queens Road

Melbourne Victoria 3004

Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 Prescription only medicine

DATE OF APPROVAL

TGA approval: Date, Month, Year.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Alendraccord Tablets 10 mg
(Alendronate Sodium Tablets 10mg)

NAME OF THE MEDICINE

Alendronate Sodium

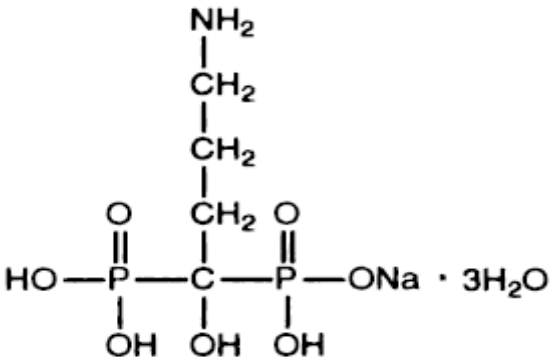
Chemical name: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

Molecular formula: $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$,

The molecular weight is 325.12

CAS Registry Number is: 121268-17-5

The structural formula is



DESCRIPTION

Alendronate sodium, is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Alendraccord Tablets (Alendronate Sodium) are available as 10mg oral uncoated tablets. Each tablet of Alendraccord contains 13.05 mg of alendronate sodium, which is the molar equivalent to 10 mg of alendronic acid. In addition to the active ingredient alendronate

sodium, each Alendraccord tablet contains the following inactive ingredients: Cellulose-microcrystalline, lactose anhydrous, croscarmellose sodium and magnesium stearate.

PHARMACOLOGY

PHARMACOKINETIC PROPERTIES

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. There was substantial variability both within and between patients, coefficient of variation 63% and 77%, respectively. Oral bioavailability in men (0.6%) was similar to that in women.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis studies, Alendronate Sodium Tablets were effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In normal subjects, oral prednisone (20 mg three times daily for five days) did not substantially alter the oral bioavailability of alendronate (alendronate alone, 0.73%; alendronate plus prednisone, 0.87%).

Distribution

Preclinical studies show that alendronate transiently distributes to soft tissues following administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of alendronate in plasma following therapeutic oral doses are generally below the limits of quantification (less than 5 ng/mL). Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolised in animals or humans.

Elimination

Following a single 10 mg IV dose of [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces; the renal clearance of alendronate was 71 mL/min.

Plasma concentrations fell by more than 95% within 6 hours following IV administration, due to distribution to the bone and excretion in the urine. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicines by those systems in humans.

Preclinical studies show that the alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found over three weeks in rats, with a cumulative IV dose of 35 mg/kg. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Bioavailability

Alendraccord 10mg tablets have been registered on the basis that they are a direct scale of a 70mg test tablet containing alendronate 70mg that has been shown to be bioequivalent to Australian-sourced Fosamax 70mg tablets in a large conventional bioequivalence study. The study was an open label, balanced, randomised, single dose, two-treatment, four period, replicate, two-sequence, two-way crossover oral bioequivalence study of alendronate sodium tablets, 70 mg (test product, B) in comparison with Fosamax® 70 mg (reference product, A) in 120 healthy adult men under fasting conditions. This study measured urinary alendronate excretion. Based on urinary excretion of alendronate, the following comparisons and statistical analyses were made:

Parameters(units)	ln-transformed Geometric Least Squares Mean			90% Confidence intervals (parametric)	Intra-subject CV (%)
	Test Product alendronate 70mg (B)	Reference Product Fosamax 70mg (A)	Ratio (B/A) %		
Max_rate (mL*ng/mL/h)	73003.869	70239.278	103.9	96.81-111.59	A 50.8 B 39.9
AURC_last (mL*ng/mL)	207129.392	187308.128	110.6	102.42-119.39	A 47.5 B 43.8
AURC_INF (mL*ng/mL)	213949.772	193042.704	110.8	102.77-119.53	A 47.9 B 43.2

The 90% CI fell within the acceptance limits of 80-125% required for bioequivalence as set out in the protocol, for all three pre-specified parameters, Max_rate (mL*ng/mL/h); AURC_last (mL*ng/mL) and AURC_INF (mL*ng/mL). Bioequivalence was therefore established.

PHARMACODYNAMIC PROPERTIES

Alendronate is a bisphosphonate that, in animal studies, localises preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass (see Clinical Trials section for details). Following exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

The relative inhibitory activities on bone resorption and mineralisation of alendronate and etidronate were compared in growing rats. The lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding safety margin for etidronate was one to one. These data indicate that,

unlike etidronate, alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

OSTEOPOROSIS

WHO utilises the definition of osteoporosis as a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. The diagnosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the gender specific mean for young adults) or by the presence or history of osteoporotic fracture. It occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Daily oral doses of alendronate in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following the discontinuation of alendronate despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with Alendronate Sodium Tablets 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with Alendronate Sodium Tablets. In osteoporosis treatment studies Alendronate Sodium Tablets 10 mg/day decreased the markers of bone formation, osteocalcin and total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months.

OSTEOPOROSIS IN MEN

Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. All men with osteoporosis should be investigated for hypogonadism and, if necessary, treated for this condition. Treatment of men with osteoporosis with Alendronate Sodium Tablets 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%.

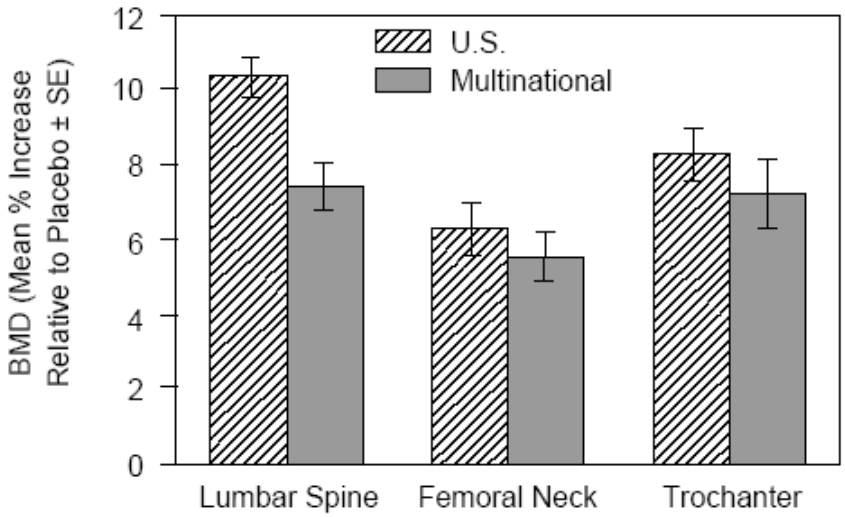
CLINICAL TRIALS

Postmenopausal women

Effect on bone mineral density

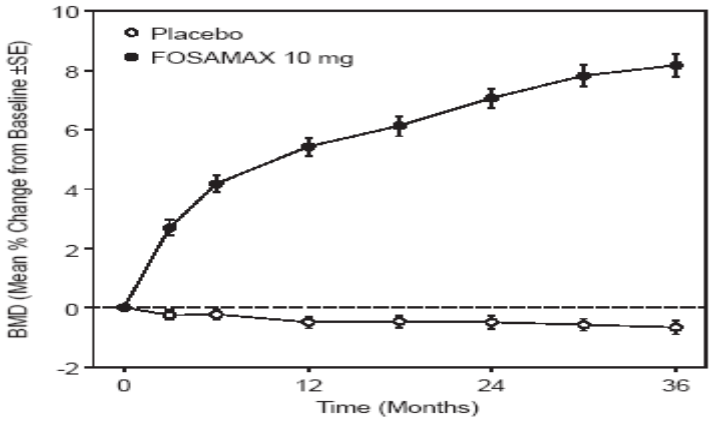
The efficacy of Alendronate Sodium Tablets 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in two large three year multicentre studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck and trochanter in patients receiving Alendronate Sodium Tablets 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Fig-1:-Increase in BMD
Alendronate Sodium Tablets 10 mg/day in Two Studies at Three Years



These increases were highly significant relative both to baseline and placebo at each measurement site in each study. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment (see figure below for lumbar spine results). In the two-year extension of these studies, treatment with Alendronate Sodium Tablets 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine 0.94%; trochanter 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, Alendronate Sodium Tablets appears to reverse the progression of osteoporosis as assessed by increased bone mineral density. Alendronate Sodium Tablets were similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use of concomitant medications.

Fig -2: Time Course of Effect of Alendronate Sodium Tablets 10 mg/day versus Placebo: Lumbar Spine BMD Percent Change from Baseline



In patients with postmenopausal osteoporosis treated with Alendronate Sodium Tablets 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those in the placebo groups. These data indicate that continuous treatment with Alendronate Sodium Tablets is required to produce progressive increases in bone mass.

The therapeutic equivalence of Alendronate Sodium Tablets once weekly 70 mg (n = 519) and Alendronate Sodium Tablets 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the70 mg once weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group.
The two treatment groups were also similar with regard to BMD increases at other skeletal sites. While there are no placebo-controlled fracture data for the once weekly 70 mg tablet, the increases in bone density support the expectation that Alendronate Sodium Tablets once weekly 70 mg will have effects to reduce the incidence of fractures similar to those of the 10 mg daily treatment (see below). The study was not designed to evaluate the relative compliance of Alendronate Sodium Tablets once weekly 70 mg and 10 mg daily.

Effect on fracture incidence

Although the US and Multinational studies (see above) were not designed to assess fracture rates as the primary endpoint, preplanned analysis of the data pooled across once daily doses at three years revealed a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with Alendronate Sodium Tablets experiencing one or more vertebral fractures (3.2%) relative to those treated with placebo (6.2 %). Furthermore, of patients who sustained any vertebral fracture, those treated with Alendronate Sodium Tablets experienced less height loss (5.9 mm vs 23.3 mm) due to a reduction in both the number and severity of fractures.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline vertebral (compression) fracture and the Four-Year Study of patients with low bone mass but without baseline vertebral fracture.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline vertebral fracture)

This randomised, double-blind, placebo-controlled 2027-patient study, (Alendronate Sodium Tablets n=1022; placebo, n=1005) demonstrated that treatment with Alendronate Sodium Tablets resulted in clinically significant reductions in fracture incidence at three years as shown in the table -1. Data also showed statistically significant reductions in painful vertebral fractures and clinical fractures at other sites. Similar reductions of hip and wrist fractures were seen in five pooled osteoporosis treatment studies of two or three years duration.

Table-1

Effect of Alendronate Tablets on fracture incidence in the three-year study of FIT (% of patients with vertebral fracture at baseline)					
	Alendronate Tablets n = 1022	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %	P Value
Patients with:					
≥ 1 new vertebral fracture	7.9	15.0	7.1	47	<.001*
≥ 2 new vertebral fractures	0.5	4.9	4.4	90	<.001*
≥ 1 painful vertebral fracture	2.3	5.0	2.7	54	<.002**
Any painful (inc. vertebral) fracture	13.8	18.1	4.3	26	0.007**
Hip fractures	1.1	2.2	1.1	51	0.047**
Wrist (forearm) fractures	2.2	4.1	1.9	48	0.013**
* Mantel-Haenzel chi^2				**Log Rank test	

Furthermore, in this population of patients with baseline vertebral fracture, treatment with Alendronate Sodium Tablets significantly reduced the incidence of hospitalisations resulting from any cause (25.0%vs. 30.7%, a 20% relative risk reduction). This difference appears to be related, at least in part, to the reduction in fracture incidence.

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline vertebral fracture)

This randomised, double-blind, placebo-controlled, 4432-patient study (Alendronate Sodium Tablets, n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to Alendronate Sodium Tablets. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table-2 for the patients with osteoporosis.

Table -2

Effect of Alendronate Tablets on fracture incidence in Osteoporotic† Patients in the four-year study of FIT (patients without vertebral fracture at baseline)				
	% of Patients			
	Alendronate Tablets n = 1545	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
≥ 1 painful fracture	12.9	16.2	3.3	22**
≥ 1 vertebral fracture††	2.5	4.8	2.3	48***
≥ 1 painful vertebral fracture	1.0	1.6	0.6	(NS)
Hip fracture	1.0	1.4	0.4	(NS)
Wrist (forearm) fracture	3.9	3.8	-0.1	None

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fracture: Alendronate Sodium Tablets, n=1426; placebo, n=1428
ns Not significant. This study was not powered to detect differences at these sites.
**p = 0.01, ***p <0.001

Consistency of fracture results

The reductions in the incidence of vertebral fractures (Alendronate Sodium Tablets vs. placebo) in the Three and Four-Year Studies of FIT were consistent with that in the combined US and Multinational (US/Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with Alendronate Sodium Tablets reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (Three-Year FIT: 47% reduction, p<0.001; Four-Year FIT: 44% reduction, p=0.001 US/Mult, 48% reduction, p=0.034). In addition, Alendronate Sodium Tablets reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the US/Mult and Three-Year FIT studies (p<0.001). Thus, Alendronate Sodium Tablets reduced the incidence of vertebral fractures whether or not patients had experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of Alendronate Sodium Tablets in reducing the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with greatest morbidity.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with Alendronate Sodium Tablets at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralisation and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in ovariectomised rats and baboons exposed to long term alendronate treatment, indicate that bone formed during therapy with Alendronate Sodium Tablets is of normal quality.

A

Concomitant Use with Oestrogen/Hormone Replacement Therapy

The effects on BMD of treatment with Alendronate Sodium Tablets 10 mg once daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomised postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or Alendronate Sodium Tablets alone (both 6.0%).

The effects on BMD when Alendronate Sodium Tablets were added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of Alendronate Sodium Tablets 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Men

The efficacy of Alendronate Sodium Tablets 10 mg once daily in men with osteoporosis was demonstrated in a two-year, double-blind, placebo-controlled, multicentre study, which enrolled 241 osteoporotic men between the ages of 31 and 87 years. All patients in the study (97.5% of whom were Caucasian) had either:1) a BMD T-score $\leq$ -2 at the femoral neck and $\leq$ -1 at the lumbar spine or 2) a baseline osteoporotic fracture and a BMD T-score of $\leq$ -1 at the femoral neck. At two years the mean increases relative to placebo in BMD in men receiving Alendronate Sodium Tablets 10 mg daily were; lumbar spine 5.3%; femoral neck 2.6%; trochanter 3.1%; and total body 1.6% (all $p \leq 0.001$). Alendronate Sodium Tablets were effective regardless of age, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with the much larger studies in postmenopausal women, in these men Alendronate Sodium Tablets 10 mg daily reduced the incidence of new vertebral fracture (post-hoc analysis; assessment by quantitative radiography) relative to placebo (0.8% vs 7.1%, respectively; $p = 0.017$) and correspondingly, also reduced height loss (-0.6 vs –2.4 mm, respectively; $p = 0.022$).

The effects of discontinuation of Alendronate Sodium Tablets treatment have not been studied in this population.

Glucocorticoid - Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip and rib). It occurs both in males and females of all ages. Bone loss occurs as a result of a lower rate of bone formation relative to that of bone resorption. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of one year's duration, Alendronate Sodium Tablets 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bonespecific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 25 to 30% and 12 to

15%, respectively. As a result of inhibition of bone resorption, Alendronate Sodium Tablets 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1%) and serum phosphate (approximately 2 to 7%).

The efficacy of Alendronate Sodium Tablets 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year placebo controlled, doubleblind, multicentre studies (n: total = 560, males = 176) of virtually identical design. Most of the patients were ambulant, caucasian and non-smokers. The study population included patients with rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, pemphigus, asthma, myositis, inflammatory bowel disease, giant cell arteritis, sarcoidosis, myasthenia gravis, chronic obstructive pulmonary disease and nephrotic syndrome. The range and duration of prior corticosteroid use in the studies was 0 to 538 months with a mean of 43.6 months and a median of 12 months. The range of prednisone dose at study commencement was 5 to 135 mg/day with a mean of 18.4 mg and a median of 10 mg daily. Fifty-seven percent of patients had osteopenia/osteoporosis at study commencement. Patients received supplemental calcium and vitamin D. At one year, the mean increases relative to placebo in BMD in patients receiving Alendronate Sodium Tablets 5 mg/day from the combined studies were: lumbar spine, 2.41%; femoral neck, 2.19%; and trochanter, 1.65%. These increases were significant at each site. Total body BMD was maintained with Alendronate Sodium Tablets 5 mg/day indicating that the increase in bone mass of the spine and hip did not occur at the expense of other sites. The increases in BMD with Alendronate Sodium Tablets 10 mg/day were similar to those with Alendronate Sodium Tablets 5 mg/day in all patients except for postmenopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with Alendronate Sodium Tablets 10 mg/day were greater than those with Alendronate Sodium Tablets 5 mg/day at the lumbar spine (4.11% vs. 1.56%) and trochanter (2.84% vs. 1.67%), but not at other sites. Alendronate Sodium Tablets were effective regardless of dose or duration of glucocorticoid use. In addition, Alendronate Sodium Tablets were similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received Alendronate Sodium Tablets at doses of up to 10 mg/day.

INDICATIONS

Indications for Alendraccord Tablets

Alendraccord Tablets 10mg are indicated for the treatment of:

- Osteoporosis*, including glucocorticoid- induced osteoporosis.

Alendraccord Tablets 10 mg are also indicated for prevention of

- Osteoporosis in post menopausal women with low bone mass (at least 1 standard deviation below the mean for young adults) not receiving oestrogen.
- Glucocorticoid- induced osteoporosis in those patients on long term corticosteroid therapy (see Clinical trials).

* Prior to treatment, osteoporosis must be confirmed by:

• the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults

or by

• the presence of osteoporotic fracture.

CONTRAINDICATIONS

- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcaemia (see PRECAUTIONS)

PRECAUTIONS

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE DOSAGE AND ADMINISTRATION. PHYSICIANS SHOULD THEREFORE BE ALERT TO ANY SIGNS OR SYMPTOMS SIGNALING A POSSIBLE OESOPHAGEAL REACTION. PATIENTS SHOULD BE INSTRUCTED TO DISCONTINUE ALENDRACCORD TABLETS AND SEEK MEDICAL ATTENTION IF THEY DEVELOP DYSPHAGIA, ODYNOPHAGIA OR RETROSTERNAL PAIN.

GENERAL

Causes of osteoporosis other than hypogonadism, aging and glucocorticoid use should be considered. If there are clinical reasons to suspect hypocalcaemia and/or vitamin D deficiency (serum levels 25 hydroxyvitamin D < 9 nmol/L), the appropriate diagnostic tests should be performed. Hypocalcaemia must be corrected before initiating therapy with Alendronate Sodium Tablets (See CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Alendronate Sodium Tablets.

Small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Alendronate, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalisation.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking Alendronate Sodium Tablets and/or who fail to swallow it with the

recommended amount of water, and/or who continue to take Alendronate Sodium Tablets after developing symptoms suggestive of oesophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION).

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when Alendronate Sodium Tablets are given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis, or ulcers.

DENTAL

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates including Alendronate Sodium Tablets (see ADVERSE EFFECTS, *Post-Marketing Experience*). As of May 2004, ONJ after bisphosphonate treatment has been described in a total of 99 cases in two large case series, 7 of which were taking oral bisphosphonates. As of 3 Nov 2006, the Australian Adverse Drug Reactions Advisory Committee has received 25 reports of ONJ in patients receiving alendronate. Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection) and smoking.

Prior to treatment with bisphosphonates, a dental examination with appropriate preventative dentistry should be considered in patients with possible risk factors.

Before commencing invasive dental procedures, patients and their dentist should be advised of the risks and reports of osteonecrosis of the jaw so that dental symptoms, including toothache, developing during treatment can be fully assessed for cause before treatment of the tooth commences.

For patients requiring invasive dental surgery (eg. tooth extraction, dental implants), there are no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Therefore clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including discontinuation of bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

In patients who develop ONJ while on bisphosphonate therapy, the clinical judgment of the treating physician should guide the management plan to include appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be based on individual benefit/risk assessment. Surgery at the affected area may exacerbate the condition.

ATYPICAL STRESS FRACTURES

A small number of long-term (usually longer than three years) alendronate-treated patients developed stress fractures of the proximal femoral shaft (also known as insufficiency fractures). Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reported cases of this condition is very low (some 40 reported cases world-wide). Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on individual benefit/risk assessment. A cause and effect relationship between bisphosphonate use and stress fractures has not been excluded.

MUSCULOSKELETAL PAIN

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see ADVERSE EFFECTS, *Post-Marketing Experience*). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

RENAL INSUFFICIENCY

Alendraccord Tablets are not recommended for patients with creatinine clearance < 35mL/min (see DOSAGE AND ADMINISTRATION).

DOSING INSTRUCTIONS FOR PATIENTS

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow each tablet of Alendraccord Tablets with a full glass of water. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take Alendraccord Tablets at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. Patients should be instructed that if they develop symptoms of oesophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking Alendraccord Tablets and consult their physician.

EFFECTS ON FERTILITY

Alendronate sodium had no effect on fertility in male and female rats at oral doses of up to 9 and 15 mg/kg/day.

USE IN PREGNANCY (Category B3)

Alendronate has not been studied in pregnant women and should not be given to them. In studies with pregnant rats, oral alendronate doses of 2 mg/kg/day and above resulted in

dystocia due to maternal hypocalcaemia. Foetal weight was reduced in rats at maternal doses greater than 5 mg/kg/day. No teratogenic effects were seen in rats or rabbits at oral doses up to 25 and 35 mg/kg/day, respectively.

Australian Categorization Definition of *Category B3 :-* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans

USE IN LACTATION

Alendraccord Tablets have not been studied in breastfeeding women and should not be given to them.

PAEDIATRIC USE

Alendraccord Tablets have not been studied in children and should not be given to them.

USE IN THE ELDERLY

In controlled trials, there was no age-related difference in the efficacy or safety profiles of Alendronate Sodium Tablets.

CARCINOGENICITY

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

GENOTOXICITY

Alendronate did not cause gene mutations in bacteria or in mammalian cells *in vitro*, nor did it cause DNA damage in rat hepatocytes *in vitro* (alkaline elution assay). In assays of chromosomal damage, alendronate was weakly positive in an *in vitro* assay using Chinese hamster ovary cells at cytotoxic concentrations (≥5mM), but was negative at IV doses up to 25 mg/kg/day (75 mg/m^2) in an *in vivo* assay (chromosomal aberrations in mouse bone marrow).

INTERACTIONS WITH OTHER MEDICINES

If taken at the same time it is likely that calcium supplements, antacids and other oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking Alendraccord tablets before taking any other oral medication.

No other drug interactions of clinical significance are anticipated though the concomitant medication with two or more bisphosphonates cannot be recommended because of the lack of clinical data.

Concomitant use of HRT (oestrogen ± progestin) and Alendronate Sodium Tablets was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of Alendronate Sodium Tablets and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see ADVERSE EFFECTS), Clinical Studies, Concomitant use with oestrogen/hormone replacement therapy).

Specific interaction studies were not performed. Alendronate Sodium Tablets (10 mg and 5 mg/day) were used in studies of treatment and prevention of osteoporosis in postmenopausal women, men and glucocorticoid users, with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions. In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of Alendronate Sodium Tablets greater than 10 mg and aspirin-containing products.

Since Non Steroidal Anti-inflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

EFFECT ON ABILITY TO DRIVE OR USE MACHINERY

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronate sodium tablets may affect some patients' ability to drive or operate machinery.
Individual responses to Alendronate Sodium Tablets may vary (see ADVERSE EFFECTS).

EFFECT ON LABORATORY TESTS

In double-blind, multicentre, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking Alendronate Sodium Tablets versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P/dL (0.65 mM) were similar in both treatment groups.

ADVERSE EFFECTS

CLINICAL STUDIES
In clinical studies Alendronate Sodium Tablets were generally well tolerated. In studies of up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

<u>Treatment of osteoporosis</u>
<u>Postmenopausal women</u>

Alendronate Sodium Tablets have been evaluated for safety in clinical studies in approximately 5000 postmenopausal patients. In two three-year, placebo controlled, double blind multicentre studies, discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with Alendronate Sodium Tablets 10 mg/day and 6.0% of 397 patients treated with placebo. Adverse experiences reported by

the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either Alendronate Sodium Tablets 10 mg/day or placebo are presented in the following table-3

Table-3

Drug Related Adverse Experiences Reported in ≥1% of Patients

	Alendronate Sodium 10mg/day % (n=196)	PLACEBO % (n=397)
Gastrointestinal		
abdominal pain	6.6	4.8
Nausea	3.6	4.0
Dyspepsia	3.6	3.5
Diarrhoea	3.1	1.8
constipation	3.1	1.8
Flatulence	2.6	0.5
acid regurgitation	2.0	4.3
oesophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distension	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

Rarely, rash and erythema have occurred.

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of Alendronate Sodium Tablets 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued Alendronate Sodium Tablets 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with Alendronate Sodium Tablets 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: Alendronate Sodium Tablets, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with Alendronate Sodium Tablets 5 or 10 mg/day.

In a one-year, double-blind, multicentre study, the overall safety and tolerability profiles of Alendronate Sodium Tablets once weekly 70 mg (n = 519) and Alendronate Sodium Tablets 10 mg daily (n = 370) were similar. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either patient group are presented in the following table-4

Table-4

Drug Related Adverse Experiences Reported in ≥ 1% of Patients

	Alendronate Tablets 70mg/day % (n = 519)	Alendronate Tablets 10mg/day % (n = 370)
Gastrointestinal		
Abdominal pain	3.7	3.0
Dyspepsia	2.7	2.2
Acid regurgitation	1.9	2.4
Nausea	1.9	2.4
Abdominal distension	1.0	1.4
Constipation	0.8	1.6
Flatulence	0.4	1.6
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Concomitant use with oestrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with Alendronate Sodium Tablets 10 mg once daily and oestrogen ± progestin (n=354) was consistent with those of the individual treatments.

Men

In a two year, placebo-controlled, double-blind, multicentre study, the safety profile of Alendronate Sodium Tablets 10 mg daily in 146 men was generally similar to that seen in postmenopausal women.

Treatment and prevention of glucocorticoid - induced osteoporosis.

In two, one-year, placebo-controlled, double-blind, multicentre studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of Alendronate Sodium

Tablets 5 and 10 mg/day were generally similar to that of placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either Alendronate Sodium Tablets 5 mg/day, 10 mg/day or placebo are presented in the following table-5:

Table -5

Drug Related Adverse Experiences Reported in ≥ 1% of Patients

	Alendronate Tablets 10mg/day	Alendronate Tablets 5mg/day	Placebo
	%	%	%
Gastrointestinal			
Abdominal pain	3.2	1.9	0.0
Acid regurgitation	2.5	1.9	1.3
Constipation	1.3	0.6	0.0
Melena	1.3	0.0	0.0
Nausea	0.6	1.2	0.6

Post-marketing Experience

The following adverse effects have been reported in post-marketing use with alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcaemia has occurred, generally in association with predisposing conditions. Rarely, peripheral
oedema.

Gastrointestinal: nausea, vomiting, oesophagitis, oesophageal erosions, oesophageal ulcers, rarely oesophageal stricture or perforation, and oropharyngeal ulceration; rarely, gastric or duodenal ulcers, some severe and with complications (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), often with delayed healing, has been reported rarely.

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see PRECAUTIONS); joint swelling, atypical stress fracture (see PRECAUTIONS).

Nervous System: dizziness, vertigo, dysgeusia.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special senses: rarely uveitis; scleritis or episcleritis.

DOSAGE AND ADMINISTRATION

Alendraccord Tablets must be taken at least 30 minutes before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water),

food and some medications are likely to reduce the absorption of alendronate (see INTERACTIONS WITH OTHER MEDICINES).

Alendraccord Tablets should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, Alendraccord Tablets should only be swallowed with a full glass of water.

Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendraccord Tablets should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experiences (see PRECAUTIONS).

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE PRECAUTIONS. PATIENTS SHOULD BE INSTRUCTED THAT IF THEY DEVELOP SYMPTOMS OF OESOPHAGEAL DISEASE (SUCH AS DIFFICULTY OR PAIN UPON SWALLOWING, RETROSTERNAL PAIN OR NEW OR WORSENING HEARTBURN) THEY SHOULD STOP TAKING ALENDRACCORD TABLETS AND CONSULT THEIR PHYSICIAN.

In clinical trials, Alendronate Sodium Tablets were administered with appropriate calcium and vitamin D supplementation. The use of vitamin D as the sole treatment of osteoporosis has not been established.

Patients should receive supplemental calcium and/or vitamin D, if intake is inadequate (see PRECAUTIONS). Physicians should consider the vitamin D intake from vitamins and dietary supplements. Additional supplements should not be taken at the same time of the day as Alendronate Sodium Tablets.

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). Alendraccord tablets are not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min).

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to Alendronate Sodium Tablets, there are no known or theoretical safety concerns related to Alendronate Sodium Tablets in patients who previously received any other antiosteoporotic therapy.

<u>Treatment of osteoporosis</u>

The recommended dosage is:

• one 10 mg tablet of Alendraccord tablets once daily

<u>Treatment and prevention of glucocorticoid - induced osteoporosis</u>

For postmenopausal women not receiving oestrogen, the recommended dosage is one 10 mg tablet of Alendraccord tablets once a day (see Clinical Trials, Glucocorticoid - Induced Osteoporosis).

OVERDOSAGE

No specific information is available on the treatment of overdosage with alendronate. Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. Administration of milk or antacids, to bind alendronate, should be considered.

Contact the Poisons Information Centre (telephone 13 11 26) for advice regarding management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Alendraccord Tablets 10 mg (AUST R 161444): White to off white, oval, biconvex tablet debossed with “10” on one side and plain on other side.

Supplied in blister packs of 30 tablets.

STORAGE CONDITIONS
Store below 25°C.

Keep the pack in a dry place and store tablets in original blister package until use.

NAME AND ADDRESS OF THE SPONSOR

Accord Healthcare Pty Ltd

Unit 702/23 Queens Road

Melbourne Victoria 3004

Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 Prescription only medicine

DATE OF APPROVAL

TGA approval: Date, Month, Year.

Therapeutic Goods Administration

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