EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/92999/2014

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC

Valebo and associated names

INNs of the active substances: Alendronic acid and alfacalcidol

Applicant: Teva Pharma B.V

Procedure no: EMEA/H/A-29/1364

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMDh 60 day procedure

Teva Pharma B.V submitted an application for decentralised procedure of Valebo and associated names, a fixed combination pack of alendronate sodium (alendronic acid) 70 mg tablets and alfacalcidol 1 µg soft capsules, on 1 September 2011.

The application was submitted to the reference Member State (RMS): Germany and the concerned Member States (CMS): Austria, Belgium, Bulgaria, Denmark, Estonia, Spain, France, Hungary, Ireland, the Netherlands, Portugal, Slovenia, Slovak Republic and the United Kingdom.

The decentralised procedure DE/H/3436/01/DC started on 1 December 2011.

On day 210, Spain's major issues on efficacy remained unsolved; hence the procedure was referred to the CMDh, under Article 29, paragraph 1 of Directive 2001/83/EC, by Spain on 11 December 2012. The CMDh 60 day procedure was initiated on 31 December 2012.

Day 60 of the CMDh procedure was on 28 February 2013 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by Germany on 28 February 2013. Spain raised public health objections to Valebo and associated names on the grounds that the role of alfacalcidol in the reduction in the fall rate has not been demonstrated. The objecting Member State argued that in order to support the inclusion of this indication the application should be based on parallel-group, randomised, double-blind, placebo or comparator controlled clinical trials with an adequate number of patients.

2. Scientific discussion during the referral procedure

2.1. Introduction

Valebo is a combination package consisting of tablets containing 70 mg of alendronic acid and soft capsules containing 1µg of alfacalcidol. Alendronic acid is a bisphosphonate with high affinity for the hydroxylapatite of the bone. Bisphosphonates have strong pharmacodynamic action on osteoclast activity. Alfacalcidol is a vitamin D analogue which acts as a regulator of calcium and phosphate metabolism. Alfacalcidol is converted rapidly in the liver to 1,25 dihydroxyvitamin D (calcitriol). Since this conversion is rapid, the clinical effects of alfacalcidol and calcitriol are expected to be similar.

Both active substances are currently authorised either as monotherapy or in association (combination pack). Alendronic acid is indicated in the treatment of postmenopausal osteoporosis (PMO). Alfacalcidol is indicated in various conditions where there is a disturbance of calcium or phosphorus metabolism.

The decentralised marketing authorisation application was submitted under Article 28(3) of Directive 2001/83/EC in accordance with Article 8(3) of Directive 2001/83/EC. The proposed indication for Valebo was "*Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures, whilst a significant reduction in the fall rate has been demonstrated for alfacalcidol in the elderly*".

During the decentralised procedure, concerned member states (CMS) expressed the opinion that the role of alfacalcidol in the reduction in the fall rate has not been demonstrated. The objecting Member

State argued that in order to support the inclusion of this indication the application should be based on parallel-group, randomised, double-blind, placebo or comparator controlled clinical trials with an adequate number of patients.

The decentralised procedure was closed on day 210, with most of the CMS agreeing with the conclusions of the reference member state except Spain which raised a potential serious risk to public health (PSRPH). A referral was thus triggered at the CMDh. The major concern raised by Spain could not be solved during the CMDh referral and the issue was therefore referred to the CHMP.

2.2. Critical evaluation

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture. The clinical symptoms of osteoporosis are vertebral and non-vertebral fractures. Vertebral fractures are seen in younger postmenopausal women; they are a primary consequence of low bone mass and poor bone quality. Non-vertebral fractures are found to be rather fall-related (> 90%) than a primary consequence of osteoporosis and reduced bone strength only. The risk for fractures in elderly patients is increased not only due to decreased bone mass and low bone quality but also because of declining physical performance which leads to an increased risk of falls. The main objective of osteoporosis treatment is to reduce the incidence of fractures and to stabilise or increase bone mass.

The applicant claimed that the combination package of the two active substances will act synergistically in the improvement of therapeutic outcome in patients suffering from PMO. The bisphosphonate alendronic acid increases bone mineral levels by inhibiting osteoclast function and therefore bone resorption. Alfacalcidol also increases bone mineral density but also has multi-factorial effects on muscle function and neuromuscular coordination, resulting in improvement of physical performance and a reduction of falls and fractures.

In order to demonstrate the role of alfacalcidol in the reduction of falls, the applicant made reference to 13 published clinical studies which support the effect of alfacalcidol alone and in combination with alendronate on the improvement of physical performance, the incidence of non-vertebral fractures and on falls (Table 1). The applicant also provided a population modelling and simulation of results to demonstrate that there is no difference between alfacalcidol and calcitriol direct treatments at appropriate and equivalent dosing. The applicant further performed a meta-analysis of trials with alfacalcidol and calcitriol investigating fallers.

Table 1: Clinical studies on alfacalcidol or calcitriol for falls or fallers and indirect endpoints such as physical performance and non-vertebral fractures

No.	Study	Treatment	Falls and/or fallers	Physical performance	Non-vertebral fractures
Alfacalcidol as monotherapy or in combination with alendronate for physical performance and balance					
1	Schacht and Ringe 2012	Alfa	--	√	--
2	Schacht and Ringe 2011	Alfa + ALN	--	√	--
3	Dukas et al. 2010	Alfa	√	√	--
4	Kaya et al. 2011	Alfa	√	√	--
Alfacalcidol as monotherapy or in combination with alendronate for the reduction of falls					
5	Dukas et al. 2004	Alfa	√	--	--
3	Dukas et al. 2010	Alfa	√	√	--
6	Gallagher 2004	Calcitriol	√	√	√
7	Ringe et al. 2007	Alfa + ALN	√	--	√
8	Ringe et al. 2012	Alfa	√	--	√
9	Ringe and Schacht 2012	Alfa	√	--	√
10	Ringe and Schacht 2013	Alfa	√	--	√
4	Kaya et al. 2011	Alfa	√	√	--
Alfacalcidol as monotherapy or in combination with alendronate for reduction of fall-related non-vertebral fractures					
8	Ringe et al. 2012	Alfa	√	--	√
7	Ringe et al. 2007	Alfa + ALN	√	--	√
9	Ringe and Schacht 2012	Alfa	√	--	√
10	Ringe and Schacht 2013	Alfa	√	--	√
11	Tilyard et al. 1992	Calcitriol	--	--	√
12	Tanizawa et al. 1992	Alfa / Calcitriol	--	--	√
13	Orimo et al. 2011	Alfa + ALN	--	--	√

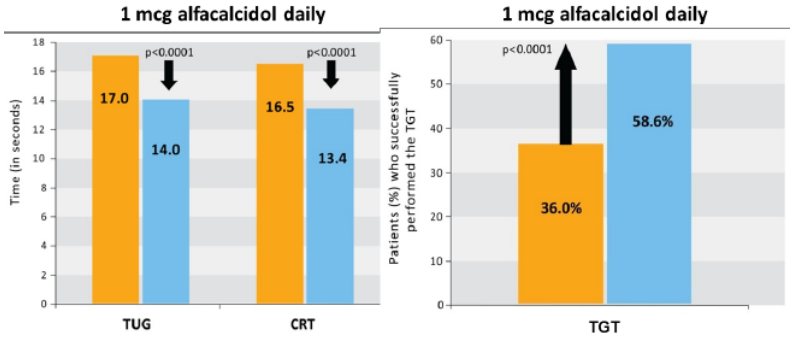
Alfa: alfacalcidol; ALN: alendronate; -- = not investigated; √ = investigated; √ = investigated / significant result

Studies on physical performance and balance

The Schacht and Ringe et al. (2012)[1] open, multi-centre, uncontrolled, prospective study assessed the effect of daily therapy with 1 µg alfacalcidol on muscle power, muscle function, balance performance and fear of falls in a cohort of 2,097 elderly patients with reduced bone mass. Patients were not preselected with regard to Vitamin D status. Already after 3 months of treatment with alfacalcidol a significant improvement in patient´s performance in the Timed Up and Go test (TUG) and Chair Rising test (CRT) was shown and a further increase by the end of the therapeutic intervention after 6 months (figure 1). After 6 months the percentage of patients who successfully performed a balance test (TGT) was also increased from 36.0 to 58.6%. The increased fear of falling on baseline was reduced by the end of the study in 74.4% of the patients.

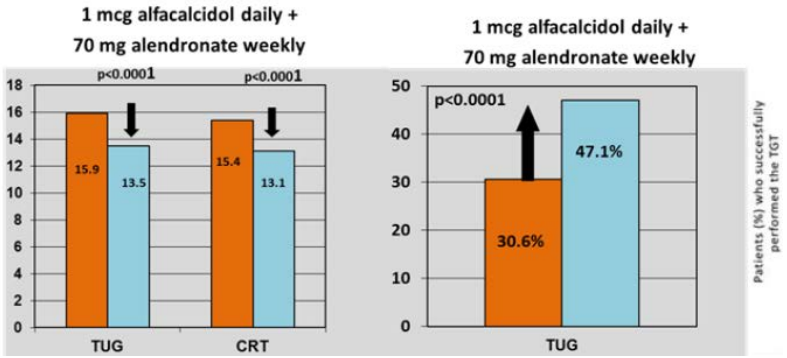
[1] Schacht E, Ringe JD. Alfacalcidol improves muscle power, muscle function and balance in elderly patients with reduced bone mass. Rheumatol Int 2012;32(1):207-15.

Figure 1: Effect of alfacalcidol monotherapy on physical performance as indirect endpoint for falls (Schacht and Ringe, 2012)



Schacht and Ringe et al. (2011)[2] investigated in an open, multi-centre, prospective study the efficacy of the product on muscle power, muscle function and balance in 2,579 elderly patients with a high risk of falls and fractures. The results showed that the percentage of patients being able to perform the CRT within 10 seconds increased from 26.3% to 42.9% after 3 months (increase 63%, p<0.0001), while successful performance of TUG within 10 seconds increased by 54% (p<0.0001) from 30.6% at onset to 47.1% after 3 months treatment. The average overall improvement of CRT was 2.3 sec (p<0.0001); for TUG it was 2.4 sec (p<0.0001) (Figure 2).

Figure 2: Effect of alfacalcidol in combination with alendronate on physical performance as indirect endpoint for falls (Schacht and Ringe, 2011)



The studies presented above demonstrated that treatment with alfacalcidol 1 µg resulted in significant increases in physical performance and balance in elderly women and men with and without an increased risk of falls as well as with and without Vitamin D insufficiency/deficiency.

Furthermore, the applicant claimed that these results on alfacalcidol monotherapy have been confirmed in a post-approval trial of the combination package 70 mg alendronate weekly and 1 µg alfacalcidol daily (Tevabone). Higher performance in functional tests is associated with a significantly lower number of fallers and risk of falls, therefore the positive effects of alfacalcidol treatment on physical performance should be considered for the assessment of the results of alfacalcidol in the reduction of falls in elderly and in patients with PMO.

Studies on reduction of falls and fallers

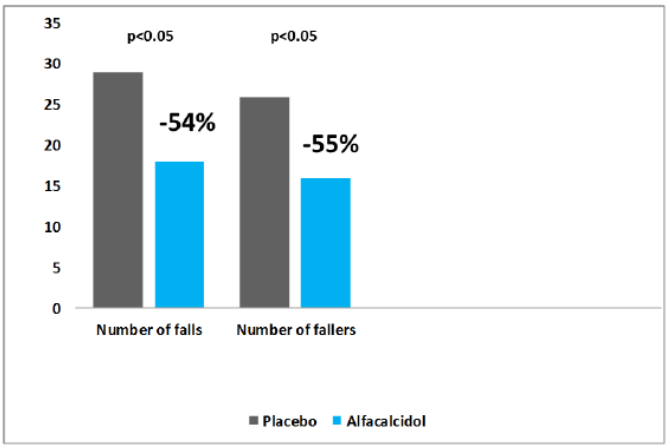
Other studies had been performed to specifically investigate the efficacy and safety of alfacalcidol mono- and combination therapy on the reduction of falls in elderly and patients with PMO.

[2] Schacht E, Ringe JD. Risk reduction of falls and fractures, reduction of back pain and safety in elderly high risk patients receiving combined therapy with alfacalcidol and alendronate: a prospective study. Arzneimittelforschung 2011; 61(1): 40-54.

Dukas et al. (2004) [3] reported about a randomised, double-blind, placebo-controlled trial investigating the effect of alfacalcidol treatment (1 µg alfacalcidol daily without supplemental calcium) on fall risk in 378 community-dwelling, Vitamin D replete/sufficient women and men aged 70 years and older. Trial duration was 36 weeks.

The results showed that alfacalcidol treatment was associated with non-significantly fewer fallers (odds ratio (OR) 0.69, 95% confidence interval (CI) = 0.41–1.16) than placebo. However, when grouping the patients according to medians of total daily calcium intake, it could be shown that significantly less falls were seen in the alfacalcidol-treated subjects with a total calcium intake of more than 512 mg/d (OR = 0.45, 95% CI = 0.21–0.97, p = 0.042) (Figure 3). In subjects with a dietary intake of less than 512 mg/ d calcium this relationship was not shown (OR = 1.00, 95% CI = 0.47–2.11, p = 0.998). Similar results were seen for the number of fallers. However, the applicant considered that insufficient calcium intake of some of the patients of this study is a very likely explanation for the lack of significant effects of alfacalcidol on falls in this subgroup, since sufficient calcium intake is considered necessary to exert efficacy of alfacalcidol.

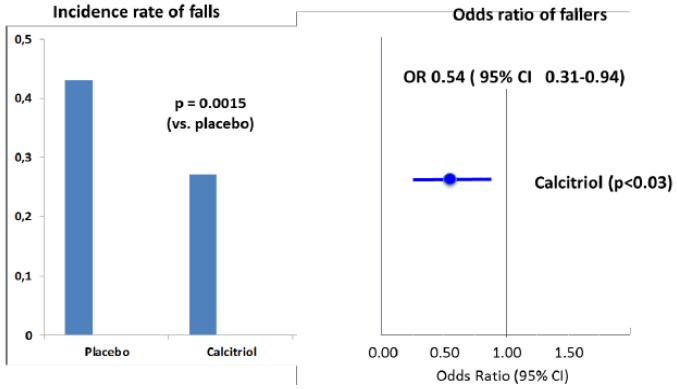
Figure 3: Number of falls / fallers after 36 weeks of treatment with alfacalcidol 1 µg/d compared to placebo in patients with > 512 mg calcium daily from diet (Dukas, 2004)



Gallagher et al. (2004)[4] examined the effects of calcitriol on falls in a randomised, double-blind, placebo-controlled study in 489 postmenopausal, Vitamin D replete/sufficient women with osteopenia. Treatment with calcitriol 0.25 µg twice daily significantly reduced the number of fallers (OR 0.54 (95% CI 0.31-0.94, p<0.03) and decreased the incidence of falls compared to placebo (0.27 versus 0.43, p=0.0015) in this 3 years trial (Figure 4). The applicant claimed that alfacalcidol 1 µg daily and of calcitriol 0.25 µg twice a day are therapeutically equivalent, and therefore they considered that the results of this randomised clinical trial can be directly extrapolated to alfacalcidol. The CHMP was of the opinion that results with calcitriol could be used as supportive data but not to conclude about the role of alfacalcidol in fall rate without confirmatory studies with alfacalcidol.

[3] Dukas L, Bischoff HA, Lindpainter LS, Schacht E, Birkner-Binder D, Damm TN, Thalman B, Stähelin HB. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004;52:230-236.
[4] Gallagher JC. The effects of calcitrol on falls and fractures and physical performance tests. J Steroid Biochem Mol Biol 2004;89-90:497-501.

Figure 4: Significant reduction in number of fallers and in incidence rate of falls by calcitriol compared to placebo (Gallagher, 2004)

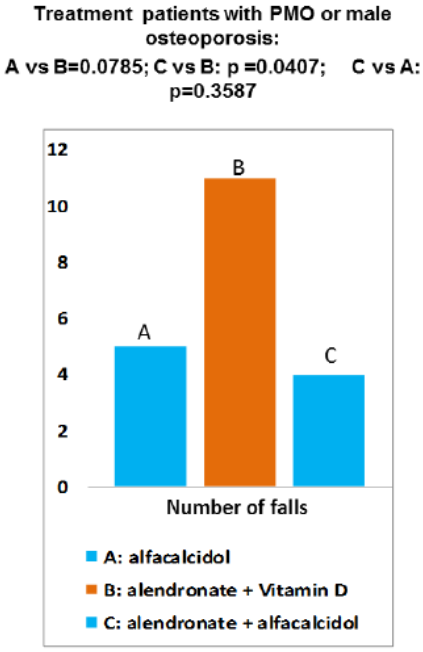


Between 2007 and 2013 Ringe et al. (2007) [5,6,7,8,9,10] investigated various aspects of alfacalcidol treatment either as monotherapy and in combination with alendronate compared to plain Vitamin D.

In 2007, they performed a randomised trial, where three treatments were compared 'alfacalcidol alone', 'alfacalcidol + alendronate' and 'alendronate + vitamin D'. In addition, 500 mg of calcium daily was added in each arm. Ninety patients (57 women, 33 men) with an average age of 66 years were included. Amongst other parameters the authors compared the rate of falls between the three groups. The combination of alendronate and alfacalcidol showed a significant superiority in reduction of falls compared to alendronate and plain Vitamin D after 2 years (Mann-Whitney (MW) = 0.5506; Confidence interval Lower bound (CI-LB) = 0.4937; p = 0.0407). The combination was not superior regarding falls to alfacalcidol alone (Figure 5). Alfacalcidol alone was slightly superior to alendronate + plain Vitamin D after 2 years (MW = 0.5422; CI-LB = 0.4838; p = 0.0785). The applicant claimed that since no significant difference in numbers of falls was found between the groups treated with the combination of 'alendronate + alfacalcidol' and 'alfacalcidol alone', this underlines the efficacy of alfacalcidol as monotherapy as well as in combination with alendronate for the reduction of falls.

[5] Ringe JD, Farahmand P, Schacht E, Rozehnal A. Superiority of a combined treatment of Alendronate and Alfacalcidol compared to the combination of Alendronate and plain vitamin D or Alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). Rheumatol Int 2007;27(5):425-34.
[6] Ringe JD, Schacht E. Improving the outcome of established therapies for osteoporosis by adding the active D-hormone analog alfacalcidol. Rheumatol Int 2007;28:103-111.
[7] Ringe JD, Schacht E, Dukas L, Mazor Z. Potency of a combined alfacalcidol-alendronate therapy to reduce the risk of falls and fractures in elderly patients with glucocorticoid-induced osteoporosis. Arzneimittelforschung 2011;61(2):104-11.
[8] Ringe JD, Schacht E. Plain Vitamin D or alfacalcidol as follow-up treatment of postmenopausal osteoporosis after continuous long term once weekly bisphosphonate intake. Osteologie 2012; 21: 83-87.
[9] Ringe JD, Farahmand P, Schacht E. Alfacalcidol in men with osteoporosis: a prospective, observational, 2-year trial on 214 patients. Rheumatol Int 2013;33(3):637-43; Epub 2012 Apr 8.
[10] Ringe JD, Schacht E. High fracture risk after long-term oral bisphosphonates and Vitamin D: Continue or switch Vitamin D to alfacalcidol. Osteology 2013;submitted for publication.

Figure 5: Number of falls after 24 months with alfacalcidol in combination with alendronate compared to plain Vitamin D in patients with established postmenopausal or male osteoporosis (Ringe, 2007)



These results are supported by two other studies published by Ringe and Schacht (2012, 2013).

In addition, the results of these studies, showing a significant reduction in fall-related non-vertebral fractures, have been confirmed by independent meta-analyses (Bischoff-Ferrari, 2004b[11]; Bischoff-Ferrari, 2009[12]; O'Donnell, 2008[13]; Richy, 2008[14]).

Population pharmacokinetic modelling and simulation at steady state

The applicant has analysed pharmacokinetics data of alfacalcidol and calcitriol dosed independently from two bioequivalence studies. The analysis was done using population pharmacokinetic modelling to confirm the exchangeability of alfacalcidol and calcitriol when administrated at appropriately scaled doses. The full population modelling and simulation analysis has demonstrated that there is no difference in calcitriol exposure at steady state after administration of either alfacalcidol or calcitriol at appropriate and equivalent dosing. Systemic levels are shown to be equivalent at steady state under scaled dosing and there is no significant difference in predicted AUC's (Area Under the Curve) at six months between alfacalcidol 1 µg once-a-day (QD) and calcitriol 0.25 µg twice-daily (BID).

Meta-analysis of trials on alfacalcidol and calcitriol investigating fallers

The applicant performed a meta-analysis of the most relevant clinical studies (Gallagher, 2004; Dukas, 2004; Ringe, 2013 and Kaya, 2011[15]) reporting the number of fallers following either alfacalcidol or calcitriol therapy. The results showed a consistent odds ratio at around 0.65 in all analyses, suggesting a reliable estimated of treatment effect as compared to placebo. The treatment effect was always

[11] Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on Falls. J Am Med Assoc 2004b;291(16):1999-2006.
[12] Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of Nonvertebral Fractures with Oral Vitamin D and Dose Dependency. Arch Intern Med 2009;169(6):551-561.
[13] O'Donnell S, Moher D, Thomas K, Hanley D A, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Mineral Metab 2008;26: 531-542.
[14] Richy F, Dukas L, Schacht E. Differential effects of D-hormone analogs and native Vitamin D on the risk of falls: A comparative meta-analysis. Calcif Tissue Int 2008;82: 102-107.
[15] Kaya U et al. Effects of Alfacalcidol on falls and balance in elderly people with Vitamin D deficiency. Turk J Phys Med Rehab 2011;57:89-93.

significant when major reported trials were analysed together. Hence, the treatment effect in a grouped meta-analysis, even with trials where “fallers” was not always the primary endpoint, remains significant independent of study design differences.

2.3. Conclusions

Having considered the data submitted by the applicant, the CHMP considered that there is sufficient evidence to conclude that in some clinical studies, alfacalcidol has been shown to reduce the risk of falls in the elderly.

The CHMP considered that the statement on falls should not be included in the section 4.1 of the SmPC. However, the CHMP agreed to provide the respective information in the section 5.1 of the SmPC “*In some clinical studies, alfacalcidol has been shown to reduce the risk of falls in the elderly”.* The package leaflet should be amended accordingly.

2.4. Benefit risk assessment and recommendation

Whereas

- The Committee considered the notification of the referral triggered by Germany under Article 29(4) of Directive 2001/83/EC. Spain considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.
- The Committee reviewed all the data submitted by the applicant in order to support the role of alfacalcidol in the reduction of the fall rate.
- The Committee is of the opinion that, based on available results of clinical trials and meta-analyses, the efficacy of alfacalcidol in combination with alendronic acid has been adequately demonstrated. However, the Committee considered that the statement on the reduction in the fall rate in the elderly should not be included in the indication. The CHMP agreed to provide the respective information in section 5.1 of the Summary of the Product Characteristics and section 1 of the package leaflet.

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure with the amendment as mentioned in Annex III for Valebo and associated names (see Annex I).