

Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

Overall summary of the scientific evaluation of Valebo and associated names (see Annex I)

Background

Valebo is a combination package consisting of tablets containing 70 mg of alendronate sodium (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. It is converted rapidly in the liver to 1,25 dihydroxyvitamin D, so called calcitriol. 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 proposed indication by the applicant for Valebo was the *"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. 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.

Evaluation

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

Studies on physical performance and balance

The open, multi-centre, prospective studies (Schacht and Ringe, 2012¹, Schacht and Ringe, 2011²) 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 of 70 mg alendronate weekly and 1 µg

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.

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.

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 fall-related non-vertebral fractures

Other studies had been performed to specifically investigate the efficacy and safety of alfacalcidol in monotherapy and combination therapy on the reduction of falls in elderly and patients with PMO (Dukas, 2004³; Gallagher, 2004⁴; Ringe, 2007⁵). These studies demonstrated the efficacy of the vitamin D analogues alfacalcidol and calcitriol on falls in elderly men and women and in postmenopausal women without diagnosed vitamin D insufficiency.

Dukas et al (2004) presented a randomised, double-blind, placebo controlled trial with 'number of fallers' as primary endpoint and an adequate number of patients. The results over 36 weeks showed that alfacalcidol treatment was associated with fewer non-significantly fallers than placebo (OR (Odds ratio) 0.69, 95% CI (confidence interval): 0.41-1.16). A post hoc analyses by medians of total calcium intake detected statistically significant differences. Significant fall reduction in alfacalcidol-treated subject with a total calcium intake of more than 512 mg/d (median Ca intake in the study) (OR 0.45; 95% CI 0.21-0.97, p=0.042) was observed but not in those with less Ca intake than 512 mg/d (OR 1.00, 95% CI 0.47-2.11, p=0.998).

Gallagher et al (2004) 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. 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.

Ringe et al (2007) presented a randomised trial, where three treatments were compared 'alfacalcidol alone', 'alfacalcidol + alendronate' and 'alendronate + vitamin D + calcium'. In addition, 500 mg of calcium daily was added in each arm. Amongst other parameters the authors compared the rate of falls between the three groups. The combination 'alendronate + alfacalcidol' showed a significant superiority in reduction of falls compared to 'alendronate + plain Vitamin D + calcium' after two years (Mann-Whitney (MW) = 0.5506; Confidence interval Lower bound (CI-LB) = 0.4937; p=0.0407) but not superiority to 'alfacalcidol alone'. Alfacalcidol alone was slightly superior to alendronate + plain Vitamin D + calcium after two 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. These results are supported by two other studies published by Ringe and Schacht (2012, 2013).

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 calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol* 2004;89-90:497-501.

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.

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, 2004b⁶; Bischoff-Ferrari, 2009⁷; O'Donnell, 2008⁸; Richy, 2008⁹).

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 administered at appropriately scaled doses. The 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, 2013¹⁰ and Kaya, 2011¹¹) 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 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.

Conclusion

Having considered that 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.

⁶ 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.

⁷ 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.

⁸ 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.

⁹ 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.

¹⁰ 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.

¹¹ 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.

Grounds for positive opinion

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).