Ibandronate 150mg oral once monthly is indicated for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures.

**BONE AND VIBE DATA SUMMARY**

Registration of a new bisphosphonate for the treatment of osteoporosis requires fracture data from a randomised, placebo-controlled, clinical trial, which has fracture reduction as its primary outcome. The primary fracture prevention trials for the currently available bisphosphonates include:

- Alendronate (10mg daily) - The Fracture Intervention Trials (FIT 1 & 2), which provided vertebral and hip fracture efficacy data.
- Risedronate (5mg daily) - The Vertebral Efficacy with Risedronate Therapy (VERT-NA and VERT-International) studies which demonstrated vertebral fracture efficacy.
- Ibandronate - The Hip Intervention Program (HIP) study demonstrated hip fracture reduction with risedronate (2.5mg daily) and ibandronate (2.5mg daily). The iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE), which demonstrated vertebral fracture efficacy. Hip fracture efficacy was demonstrated in high-risk patients.
- Zoledronate (yearly IV) - The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) trial, which demonstrated both vertebral and hip fracture reduction.

**Ibandronate - The primary fracture prevention trial (BONE)**

The BONE study is the primary fracture prevention trial for oral ibandronate 2.5mg daily in postmenopausal women with osteoporosis and showed a significant (62%) reduction in the risk of new vertebral fractures with ibandronate 2.5mg daily over the 3-year study duration. The BONE trial was, however, relatively small and did not show hip fracture reduction.

However, a posthoc analysis in a higher-risk subgroup of patients (T-score <-3) did show a 69% relative risk reduction in non-vertebral fractures.

It is important to note that hip fracture reduction in a higher risk subgroup of patients has been accepted both locally and internationally as adequate data for the purposes of registration.

**Ibandronate - The non-inferiority studies for the longer dosing regimens**

The European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) suggest that to register a different dosing regimen (e.g. weekly or monthly) of a bisphosphonate that has previously demonstrated efficacy in primary fracture prevention trials, ‘bridging studies’ using surrogate endpoints for fracture such as changes in BMD should be used. In other words, it is not necessary to reevaluate fracture prevention in order to obtain registration for a longer dosing regimen. It is accepted that if BMD gains of the comparator are non-inferior to the originator (within a predetermined range), then fracture efficacy can be expected to be similar.

The Monthly Oral iBandronate in LadiEs (MOBILE) trial was a non-inferiority BMD study that compared the efficacy and safety of three once-monthly oral ibandronate regimens with the ibandronate 2.5mg daily regimen.

Oral ibandronate 150mg once monthly provides twice the annual cumulative exposure to ibandronate compared to the 2.5mg daily formulation. The efficacy of this increased dose was examined in the pivotal registration study (MOBILE), in which BMD gains were significantly greater with monthly oral ibandronate than with daily ibandronate. (See section on MOBILE and MOBILE LTE).

Similarly, the Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention (MOTION) study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis showed that the two regimens were comparable at increasing BMD after 12 months at both the lumbar spine and total hip.

**Ibandronate - The VIBE database study**

No prospective head-to-head trials comparing the anti-fracture efficacy of the currently marketed weekly and monthly bisphosphonates have been done, due to the large sample size these studies would require to reliably detect differences in fracture risk, and the associated high costs. For this reason, observational database studies are increasingly being used as such studies can provide sufficient sample sizes and permit the comparison of marketed doses. Furthermore, it is unlikely that future fracture efficacy trials of bisphosphonate versus placebo will be conducted as it would be unethical to randomise patients to placebo.

The eValuation of IBandronate Efficacy (VIBE) head-to-head database fracture study compared fracture rates (hip, non-vertebral, vertebral and any clinical fracture) adjusted for confounding factors, over one year, between patients treated with monthly ibandronate 150mg orally and weekly oral bisphosphonates (alendronate, risedronate or a combined alendronate/risendronate group).

The results showed that fracture risk was not significantly different between patients receiving monthly ibandronate or weekly bisphosphonates for hip, non-vertebral or any

**IN SUMMARY, WITH RESPECT TO FRACTURE DATA:**

- Oral daily ibandronate has demonstrated a 62% relative risk reduction in vertebral fractures versus placebo in a primary study (i.e. the BONE study).
- Monthly ibandronate 150mg orally has demonstrated a significantly lower rate of vertebral fractures versus weekly oral bisphosphonates (VIBE study).
- Vertebral fracture IBN > ALN + RIS
- Monthly ibandronate 150mg orally has demonstrated comparable rates of non-vertebral and hip fractures versus weekly bisphosphonates (VIBE study).
- Non-vertebral and hip fracture IBN = ALN + RIS
- Monthly oral ibandronate may be considered noninferior with respect to hip fracture compared to the other oral bisphosphonates

*IBN - Ibandronate; ALN - Alendronate; RIS - Risedronate*
clinical fracture. However, monthly ibandronate-treated patients had a significantly lower risk of vertebral fracture than weekly bisphosphonate patients.

**BMD NON-INFERIORITY STUDIES**

The MOBILE study was a prospective, randomised, phase III, non-inferiority study that compared the efficacy and safety of three once-monthly oral ibandronate doses (50+50mg monthly, given on two consecutive days; 100mg monthly; 150mg monthly) with 2.5mg daily ibandronate, which has previously been shown to reduce vertebral fracture risk versus placebo. The study was conducted in 1609 women aged 55 to 80 years, who were at least 5 five years postmenopausal and had T-scores between <-2.5 and >-5.0. The primary endpoint of the MOBILE study was the percentage change from baseline lumbar spine bone density at one year. Reginster J-Y et al (2006) discussed the 2-year MOBILE data to confirm the one-year results and to provide more extensive safety data. Secondary endpoints included the percentage change from baseline in lumbar spine and proximal femur densities over 2 years and the percentage change in serum concentrations of the biochemical marker of bone resorption, C-telopeptide of the ß-chain of type I collagen (sCTX) from baseline. Substantial increases in lumbar spine BMD were seen in all treatment arms. It was confirmed that all once-monthly oral ibandronate regimens were at least as effective as daily treatment, and in addition, 150mg once monthly showed superiority at the lumbar spine in terms of BMD gains (p<0.001).

Substantial increases in proximal femur (total hip, femoral neck, trochanter) BMD were also seen, with 150mg once monthly producing the most pronounced effect (p<0.05 vs daily treatment). Pronounced decreases in sCTX were maintained throughout the study. Although this study did not assess fracture efficacy, the incidence of clinical fractures was similar in all treatment groups.

In terms of adverse events, the incidence of upper gastrointestinal (GI) adverse events was similar across the treatment arms (20 to 26%) and events were generally mild to moderate in severity. The incidence of flu-like illness was higher with the 150mg monthly dosing (3.3%) compared with the other dosing regimens (0.3%-1.3%). However, none of the patients experiencing flu-like illness during year 1 had a recurrence during year 2 and the 2-year results confirm a low incidence of flu-like illness with ibandronate, similar to that seen with other oral bisphosphonates.

Overall, it was concluded that once-monthly oral ibandronate is at least as effective and well tolerated as daily oral treatment. In addition, once-monthly administration may be more convenient for patients and improve therapeutic adherence, thereby optimising outcomes.

The long-term efficacy and safety of once-monthly ibandronate was studied in the extension to the two-year MOBILE study, the MOBILE-LTE. In the long-term extension (LTE), 344 patients from MOBILE monthly ibandronate arms and 698 patients from all arms were reallocated to ibandronate 100mg monthly or 150mg monthly for a further three years. The primary endpoint was the change in lumbar spine BMD from month 24 to month 60. A secondary efficacy endpoint was the change in proximal femur BMD from the end of the two-year MOBILE study (month 24) to completion of the MOBILE-LTE at month 60. The primary focus of the study, however, was the change in lumbar spine BMD from MOBILE baseline to end of five years.

The 344 patients receiving monthly ibandronate showed increases over five years in lumbar spine BMD (8.4% with 150mg once-monthly) from MOBILE baseline. Total hip BMD increased at 12 and 24 months compared to MOBILE baseline in both the 150mg monthly and the 100mg monthly treatment groups, but a plateau was reached between 24 and 36 months with no further increases. Only small changes in BMD were seen at the femoral neck and trochanter. Decreases in sCTX and procollagen type 1 amino-terminal propeptide (P1NP) seen in the 2-year MOBILE results were maintained over five years.

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**The first once monthly tablet for postmenopausal osteoporosis**

The first in its class

1 tablet monthly

Lower risk of vertebral fractures vs. weekly bisphosphonates

- 12 tablets a year vs. 52 with current weekly bisphosphonates
- Sustained low clinical fracture rate over 5 years of treatment
- Maintained lumbar spine BMD with further gradual increases up to 5 years
- Well-tolerated with a proven 5-year safety profile

BMD = Bone Mineral Density

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In terms of adverse events, the incidence of gastrointestinal events in MOBILE LTE was lower than in the MOBILE study (about 7.4% in each treatment group).

Joint pain was reported in 4% of patients receiving ibandronate 150mg. In terms of serious adverse events, there was no evidence of renal compromise and there were no symptoms suggestive of osteonecrosis of the jaw (ONJ).

The conclusion of the MOBILE-LTE study was that 150mg once-monthly ibandronate was a safe and well-tolerated treatment for postmenopausal osteoporosis. The BMD at the proximal femur is maintained, with further small gains in lumbar spine BMD. The efficacy of ibandronate once monthly is sustained over five years and there were no new safety signals.

HARRIS META-ANALYSIS
In the Harris ST et al meta-analysis, individual patient data from four phase III (BONE, IV fracture prevention, MOBILE and Dosing Intravenous Administration [DIVA]) studies were grouped into three dose levels based on annual cumulative exposure (ACE), defined as the annual dose (mg) x bioavailability (0.6% oral, 100% IV).

Inclusion criteria required 1-4 prevalent vertebral fractures, lumbar spine BMD and a T-score of -2 to -5.

The MOBILE and DIVA studies were active-controlled two-year BMD studies. Inclusion criteria did not require prevalent vertebral fractures, lumbar spine BMD but did require a T-score of -2.5 to -5.

The primary endpoint for high vs low doses of ibandronate assessed the efficacy of high vs low doses of ibandronate on non-vertebral fractures (humerus, clavicle, wrist, pelvis, hip and leg). Eight randomised treatment trials were considered for inclusion. Treatment trials were defined as those trials in which baseline lumbar spine T-score was ≤-2.5, or the baseline prevalent vertebral fracture rate was >20%, or the mean age of participants was over 60 years.

Only two trials were selected for inclusion as they provided data on prevalent vertebral fractures and data on both higher and lower doses of ibandronate.

The Kaplan-Meier plot of time to vertebral fracture risk vs placebo for key NVFs, all NVFs and all clinical fractures at two years.

CRANNEY POOLED ANALYSIS
The Cranney pooled analysis of ibandronate assessed the efficacy of high vs low doses of ibandronate on non-vertebral fractures (humerus, clavicle, wrist, pelvis, hip and leg) defined as the annual dose (mg) x bioavailability (0.6% oral, 100% IV).

In the Cranney pooled analysis of ibandronate compared with placebo, the hazard ratio for non-vertebral fracture for higher versus lower doses was 0.82. In the Cranney pooled analysis of ibandronate versus placebo, the hazard ratio for non-vertebral fracture was 0.77.

References available on request.

In summary, higher doses of ibandronate significantly reduced the risk of NVFs in this pooled analysis. However, data on prevalent vertebral fracture is not available for all studies, plus the pooled analysis does not provide enough data in order to comment on effect on hip fractures because NVF rate does not correlate with hip fracture rate.

IBANDRONATE - LONG-TERM DATA
Ibandronate is a nitrogen-containing bisphosphonate. It has an increased potency compared to alendronate and risedronate and a higher bone affinity compared to clodronate and risedronate.

Ibandronate offers greater ease of use compared with several other bisphosphonates. It is suitable for both oral and IV administration.

The long-term safety and efficacy data for the currently available bisphosphonates are as follows:

- Alendronate - 10 years, based on the Fracture Intervention Trial Extension
- Risedronate - seven years, based on the Efficacy with Risedronate (VERT) trial extension
- Zoledronate - nine years, based on the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial extension
- Ibandronate - five years, based on the MOBILE-LTE study.

Efficacy and safety of ibandronate has been demonstrated over five years:

- Observational data over 12 months suggest that ibandronate is superior to alendronate and risedronate in vertebral fracture prevention.
- Observational data over 12 months suggest that ibandronate is equal to alendronate and risedronate in non-vertebral fracture reduction.

The 344 patients receiving monthly ibandronate showed increases over five years in lumbar spine BMD (8.4% with 150mg once-monthly) from MOBILE baseline.

In terms of adverse events, the incidence of gastrointestinal events in MOBILE LTE was lower than in the MOBILE study (about 7.4% in each treatment group).

Joint pain was reported in 4% of patients receiving ibandronate 150mg. In terms of serious adverse events, there was no evidence of renal compromise and there were no symptoms suggestive of osteonecrosis of the jaw (ONJ).

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Only two trials were selected for inclusion as they provided data on prevalent vertebral fractures and data on both higher and lower doses of ibandronate.

Several doses in addition to the ones used in clinical practice were included in the analysis. As in the Harris meta-analysis, the annual cumulative exposure (ACE) was used to categorise doses as high (≥10.8mg) and low (<7.2mg).

The results showed that combining higher ACE doses of ≥10.8mg vs ACE doses of 5.5mg resulted in a hazard ratio of 0.62 or a 38% reduction in the incidence of non-vertebral fractures.

There was also a dose-response effect seen with increasing ACE doses (72-12mg) compared with ACE of 5.5mg, with hazard ratios ranging from 0.746-0.573.

An ACE of 12mg resulted in a 43% reduction in NVF risk.

An ACE ≥10.8mg resulted in a 38% reduction in NVF risk.

An ACE ≥7.2mg resulted in a non-significant NVF reduction of 25%.

The Kaplan-Meier plot of time to non-vertebral fracture for higher versus lower ACE ibandronate doses shows that higher doses prolong the time to non-vertebral fractures compared with lower doses.

In summary, higher doses of ibandronate significantly reduced the risk of NVFs in this pooled analysis. However, data on prevalent vertebral fracture is not available for all studies, plus the pooled analysis does not provide enough data in order to comment on effect on hip fractures because NVF rate does not correlate with hip fracture rate.

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