Cost-effectiveness of romosozumab (Evenity®) for the treatment of severe osteoporosis in women who are postmenopausal and are at high risk of fracture.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of romosozumab (Evenity®). Following assessment of the Applicant's submission, the NCPE recommends that romosozumab (Evenity®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (UCB Pharma S.A.) Health Technology Assessment of romosozumab (Evenity®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2022**

Summary

In July 2022, UCB Pharma S.A. submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of romosozumab (Evenity®) for the treatment of severe osteoporosis in women who are postmenopausal and are at high risk of fracture. UCB Pharma S.A. are seeking reimbursement of romosozumab on the High Tech Drug Arrangement (HT). Final data was submitted by the Applicant in December 2022.

Osteoporosis is a chronic disease characterised by low bone mass, deterioration of bone tissue, and disruption of bone microarchitecture; this can lead to compromised bone strength. The most common manifestation of osteoporosis is fracture. Fragility fractures are fractures which result from low-energy trauma, such as a fall from standing height or less. Diagnostic criteria for osteoporosis are based on bone mineral density (BMD) measurements. The BMD of an older person is compared with the BMD of a young, healthy population of the same sex (referred to as the 'young adult mean'). The result is expressed in standard deviation (SD) units and is referred to as a BMD T-score. The World Health Organisation (WHO) define osteoporosis as occurring where the BMD T-score is at least 2.5 SD below the young adult mean (−2.5 SD or lower). Severe osteoporosis is defined as a BMD T-score 2.5 SD or more below the young adult mean, in the presence of one or more fragility fractures.

Romosozumab is a humanized monoclonal antibody, and a first-in-class sclerostin inhibitor. Sclerostin inhibits the Wnt signalling pathway, which is responsible for the promotion of bone formation and suppression of bone resorption. Romosozumab is formulated as a solution for subcutaneous injection in a pre-filled pen. Each pre-filled pen contains 105mg of romosozumab. The recommended dose is 210mg (administered as two subcutaneous injections of 105mg each) once every month for 12 months.

The Applicant anticipates that romosozumab will be prescribed for women who are postmenopausal, with severe osteoporosis, who have experienced a major osteoporotic fracture (MOF) within the previous 24 months and who are, therefore, at imminent risk of another fragility fracture. This is a subpopulation of the product licence. MOFs include fractures of the total hip (including pelvis), vertebrae, distal radius and proximal humerus.

Teriparatide biosimilar was identified as the most relevant comparator to romosozumab for this assessment. Other osteoporosis treatments, including the original teriparatide biologic (Forsteo®), denosumab (Prolia®), zoledronic acid, and alendronate, were also considered.

1. Comparative effectiveness of romosozumab

Clinical evidence informing the efficacy and safety of romosozumab, in women who are postmenopausal, is available from three pivotal, phase III clinical trials.

FRAME (n=7,180) was a randomised, double-blind trial comparing romosozumab (n=3,589) to placebo (n=3,591). Following completion of a 12-month double-blind treatment period, all participants subsequently received open-label treatment with denosumab for an additional 12 months. Eligible participants were women who were postmenopausal, aged between 55 and 90 years, and who had a diagnosis of osteoporosis (defined as a BMD T-score of −2.5 SD or lower at the total hip or femoral neck). The co-primary endpoints were incidence of new vertebral fracture through to months 12 and 24. Relative risk reductions (RRRs) of 73% (95% confidence interval [CI] 53% to 84%) and 75% (95% CI 60% to 84%) in the incidence of new vertebral fracture through months 12 and 24, respectively, were observed in participants assigned to romosozumab compared to those assigned to placebo. The results were statistically significant ($p<0.001$).

ARCH (n=4,093) was a randomised, double-blind trial comparing romosozumab (n=2,046) to alendronate (n=2,047). Following completion of a 12-month double-blind treatment period, all participants subsequently received open-label treatment with alendronate for an additional 12 months. Eligible participants were women who were postmenopausal, aged between 55 and 90 years, with osteoporosis and either:

- a BMD T-score of −2.5 SD or lower at the total hip or femoral neck, and at least one moderate or severe vertebral fracture or at least two mild vertebral fractures; or
- a BMD T-score of −2.0 SD or lower at the total hip or femoral neck and at least two moderate or severe vertebral fractures, or a fracture of the proximal femur that occurred within three to 24 months prior to randomisation.

The co-primary endpoints were incidence of new vertebral fracture through month 24, and incidence of a clinical fracture (non-vertebral and symptomatic vertebral fracture) through the primary analysis. A RRR of 50% (95% CI 34% to 62%) in the incidence of new vertebral

fracture through to month 24 was observed in participants assigned to romosozumab compared to those assigned to alendronate. For incidence of clinical fracture through the primary analysis period, a RRR of 27% (95% CI 12% to 39%) was observed. For both co-primary endpoints, the results were statistically significant (p<0.001).

STRUCTURE (n=436) was a 12-month, randomised, open-label trial comparing romosozumab (n=218) to teriparatide (n=218). Eligible participants were women who were postmenopausal, aged between 55 and 90 years, with osteoporosis who had taken an oral bisphosphonate (e.g. alendronate or risedronate) for at least three years before screening, including alendronate for one year immediately before screening. Participants were also required to have a BMD T-score of −2.5 SD or lower and a history of previous fracture. The primary endpoint was percentage change from baseline in hip BMD at the total hip through month 12. The percentage change observed in patients assigned to romosozumab (+2.6%) was greater than in those assigned to teriparatide (- 0.6%); treatment difference 3.2% (95% CI 2.7% to 3.8%; p<0.0001).

Direct comparative evidence was not available for all comparators. The Applicant conducted a series of network meta-analyses (NMAs) to generate indirect comparative evidence to inform the economic model. Results from the NMAs indicate that romosozumab is associated with statistically significant improvements regarding fracture outcomes when compared to placebo. No statistically significant differences were noted when compared with teriparatide. An important limitation of the Applicant's evidence synthesis relates to heterogeneity between the clinical trials informing the NMAs. Differences in clinical trial design, baseline characteristics of patients recruited to the trials (mean age, BMD T-scores, fracture history, treatment history), and timing of endpoints were identified. Results from the NMAs should, therefore, be interpreted with caution.

2. Safety of romosozumab

The safety profile of romosozumab, in the female population with osteoporosis, was evaluated in two integrated analyses. One analysis was an evaluation across four placebo-controlled studies (FRAME, NCT00896532, NCT01992159, and BRIDGE) which compared romosozumab 210mg once every month with placebo over a 12-month treatment period. The second integrated analysis was across seven clinical trials (FRAME, ARCH, STRUCTURE,

BRIDGE, NCT02016716, NCT00896532 and NCT01992159), exposing more than 7,500 patients to romosozumab.

Across both pooled safety analysis sets, the incidence of treatment emergent adverse events (TEAEs) was similar in patients treated with romosozumab compared to control (which may have been either placebo, alendronate or teriparatide). The most commonly reported TEAEs were nasopharyngitis, arthralgia, headache, muscle spasms, cough, peripheral oedema, and neck pain. However, incidence of these TEAEs were similar across all treatment arms. Injection site reactions and cataracts were noted to be more commonly reported in patients treated with romosozumab compared to in those treated with control.

During the 12-month double blind treatment period in the ARCH trial, an imbalance in positively-adjudicated cardiovascular serious adverse events was observed between patients receiving romosozumab and alendronate (2.5% versus 1.9%, respectively). This imbalance specifically related to cardiac ischaemic (0.8% versus 0,3%) and serious cerebrovascular (0.8% versus 0.3%) events. The imbalance in major cardiovascular events continued to be observed through to at least month 24 of the follow-up period. Similar findings were not observed in the placebo-controlled FRAME trial. Due to uncertainty regarding potential increased cardiovascular risk, romosozumab is contraindicated for use in patients with a history of myocardial infarction or stroke.

3. Cost effectiveness of romosozumab

Cost-effectiveness was assessed from the perspective of the HSE using a Markov model with individual patient simulation (micro-simulation) with a lifetime horizon. This type of model allows for multiple fractures per patient and competing risks. The population considered in the model was women who are postmenopausal, with severe osteoporosis, who have experienced a MOF within the previous 24 months and who are at imminent risk of another fragility fracture. This is a subpopulation of the product licence. The modelled intervention was 12-months' treatment with romosozumab followed by 48-months' treatment with once a week oral alendronate (romosozumab/alendronate). The most relevant comparator was teriparatide biosimilar which was modelled as 24-months' treatment with teriparatide biosimilar followed by 36-months's treatment with once a week oral alendronate

(teriparatide/alendronate). Additional comparators were: the original teriparatide biologic (Forsteo®), denosumab (given for 60 months), intravenous zoledronic acid (given for 60 months), and oral alendronate (given for 60 months).

The model consisted of five mutually exclusive health states: At Risk; Hip Fracture; Vertebral fracture; Non-hip, non-vertebral (NHNV) fracture; and Death. The main clinical outcome measured in the model was incidence of fracture events. The risk of sustaining a fracture in the model depended on three elements: the risk for an individual in the general population incurring a fracture, the increased fracture risk associated with osteoporosis (the relative risk), and a risk reduction attributed to a treatment. The FRAX algorithm was used to measure risk. The incidences of hip fractures were based on Kanis et al. (2012), a large systematic review of worldwide incidences of hip fracture. The Irish clinical vertebral fracture incidence was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture in a Swedish-based study is similar to that of Ireland. The same imputation via hip fracture incidence and Swedish risk of "other fractures" was made for the combined incidence of "other fractures" in Ireland. The efficacy estimates for romosozumab/alendronate versus alendronate alone were determined from the fracture endpoints from the ARCH study. The NMA was used to conduct a comparison between romosozumab/alendronate and teriparatide/alendronate, as well as scenario analyses versus other relevant comparators.

The model also included two key assumptions. The first assumption was patient persistence to treatment; that is, how likely a patient was to continue treatment with the drug (intervention or comparator). For the Applicant's base case, persistence to treatment was informed by a Delphi panel comprised of 18 clinicians based in the United Kingdom. A second assumption related to duration of treatment effect following cessation of therapy (treatment offset). Health related quality of life (HRQoL) was informed by the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS). Costs and resources included in the model were drug acquisition costs, costs associated with general disease management, costs associated with the acute and long-term management of fracture events, and adverse event costs.

Results of the Applicant's base case cost-effectiveness analysis is presented in Table 1.

Table 1: Deterministic results of the Applicant's base-case analysis

Intervention	Total costs (€)	Total QALYs	Inc. costs (€)	Inc. QALYs	ICER *vs* baseline (€ per QALY)
Romosozumab / alendronate[1]	42,018	6.733	-	-	-
Teriparatide (biosimilar)§ / alendronate[2]	42,337	6.697	-318	0.036	Romosozumab / alendronate[1]: DOMINANT
Teriparatide (Forsteo®) / alendronate[3]	42,383	6.697	-365	0.036	Romosozumab / alendronate[1]: DOMINANT
Alendronate 60 months	38,789	6.631	3,229	0.102	31,778
Denosumab 60 months	38,550	6.678	3,468	0.055	62,780
Zoledronic acid 60 months	39,319	6.661	2,699	0.071	37,830

ICER: incremental cost-effectiveness ratio; **inc.:** incremental; **QALY:** quality adjusted life year

[1] Romosozumab 12 months followed by alendronate 48 months

[2] Teriparatide (biosimilar)§ 24 months followed by alendronate 36 months

[3] Teriparatide (Forsteo®) 24 months followed by alendronate 36 months

Interventions that are dominant are less expensive and more effective than the comparator.

A discount rate of 4% is applied to costs and outcomes.

Figures presented are rounded; results may not be directly replicable.

§ A commercial in confidence Patient Access Scheme (PAS) is in place for teriparatide biosimilar, not incorporated in these results.

To derive the NCPE-adjusted base case, the Review Group made changes to the assumptions regarding persistence to treatment, and treatment offset. The Review Group had concerns regarding the use of the DELPHI panel to inform persistence to treatment due to inconsistency of clinical opinion. Alternatively, the Review Group used a study by Morley et al, which examined persistence and compliance with osteoporosis therapies among women who are postmenopausal in a large UK database (the UK Clinical Practice Research Datalink), to inform this assumption. The Review Group were concerned regarding the sensitivity of cost-effectiveness results on the assumption of treatment offset, which lacked strong supportive evidence. The Review Group removed the assumption of treatment offset in the NCPE adjusted base case. Results of the NCPE adjusted base case are presented in Table 2.

Table 2: Deterministic results for NCPE adjusted base case analysis

Intervention	Total costs (€)	Total QALYs	Inc. costs (€)	Inc. QALYs	ICER *vs* baseline (€ per QALY)
Romosozumab / alendronate[1]	44,255	6.682	-	-	-
Teriparatide (biosimilar)§ / alendronate[2]	43,415	6.673	839	0.009	97,432

Teriparatide (Forsteo®) / alendronate[3]	43,462	6.673	792	0.009	89,664
Alendronate 60 months	39,260	6.628	4,995	0.054	92,524
Denosumab 60 months	39,092	6.661	5,162	0.021	247,387
Zoledronic acid 60 months	39,902	6.645	4,353	0.037	116,311

ICER: incremental cost-effectiveness ratio;; **QALY:** quality-adjusted life year

[1] Romosozumab 12 months followed by alendronate 48 months

[2] Teriparatide (biosimilar)§ 24 months followed by alendronate 36 months

[3] Teriparatide (Forsteo®) 24 months followed by alendronate 36 months

A discount rate of 4% is applied to costs and outcomes

Figures presented are rounded; results may not be directly replicable.

§ A commercial in confidence Patient Access Scheme (PAS) is in place for teriparatide biosimilar, not incorporated in these results.

The Review Group conducted scenario analyses to explore the sensitivity of cost-effectiveness results to changes in various assumptions. The Review Group considered cost-effectiveness results to be unstable and sensitive to small changes in incremental quality adjusted life years.

Probabilistic sensitivity analyses were conducted on both the Applicant and NCPE-adjusted base cases. For the Applicant's base case, the probability of romosozumab being cost-effective versus teriparatide biosimilar is 98% at the €20,000 per QALY threshold, and 99% at the €45,000 per QALY threshold. For the NCPE-adjusted base case, the probability of romosozumab being cost-effective, versus teriparatide biosimilar, is 4% at the €20,000 per QALY threshold and 26% at the €45,000 per QALY threshold.

4. Budget impact of romosozumab

The price to wholesaler, per pack of two romosozumab 105mg pre-filled pen, is €526.00. The cost per patient to the HSE (incorporating mark-up, Framework Agreement rebate, and patient care fees) for a 12-month treatment course of romosozumab, assuming 100% compliance, is €8,640 including VAT (€7,072 excluding VAT).

For the budget impact analysis, the Applicant considered only women who were postmenopausal with severe osteoporosis who have experienced a MOF within the previous 24 months, and who are therefore at imminent risk of another fragility fracture. This is a subpopulation of the product licence; budget impact estimates considering the broader population defined by the product licence would be higher. Comparator treatments included teriparatide biosimilar, the original teriparatide biologic (Forsteo®), denosumab

and intravenous zoledronic acid. The Applicant estimated that approximately 2,026 women would be eligible for treatment in year one, rising to 3,544 in year five. Of those eligible, the Applicant estimated that four women would be treated with romosozumab in year one rising to 868 in year five. The Applicant's estimated five-year cumulative gross- and net-drug budget impact estimates for romosozumab (including VAT) were €15.2 million and €3.2 million, respectively. The Applicant also included cost-offsets, which assumed a reduction in resource use secondary to reduced incidence of fragility fractures as a result of being prescribed pharmacological treatment. The five-year cumulative net healthcare budget impact for romosozumab (including VAT) was estimated to be €3.8 million.

The Review Group had concerns regarding the Applicant's estimates of number of patients to be treated with romosozumab. A notable difference in the magnitude of market share estimates for romosozumab, between the Applicant's Rapid Review and Health Technology Assessmnet submission, was identified by the Review Group. To explore this uncertainty, a scenario analysis was conducted using the market share values for romosozumab originally presented in the Applicant's Rapid Review submission. The five-year cumulative gross-, net-drug, and net-healthcare budget impact estimates for romosozumab (including VAT) increased to €32.1 million, €8.8 million, and €8.1 million, respectively.

Deterministic sensitivity analyses demonstrated budget impact estimates for romosozumab to be sensitive to estimated patient numbers (which the Review Group consider to be highly uncertain). Furthermore, as the Applicant only considered a subpopulation of the product licence for the budget impact estimates, patient number and expenditure would be much higher if prescribing is not contained as such.

5. Patient organisation submission

A patient organisation submission, from the Irish Osteoporosis Society, was received during the course of this assessment. This will be provided to the HSE.

6. Conclusion

The NCPE recommends that romosozumab (Evenity®), for the treatment of women who are postmenopausal with severe osteoporosis who have experienced a MOF (hip, vertebrae, distal radius, proximal humerus) within the previous 24 months and who are at imminent

risk of another fragility fracture, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*