Sammendrag av bytte – Terrosa og Forsteo

Preparat (biotilsvarende og referanse)	Biotilsvarende: **Terrosa** • Injeksjonsvæske, oppløsning, ampulle i penn Terrosa leveres i pakninger med 1 eller 3 ampulle(r). Hver sylinderampulle inneholder 2,4 ml injeksjonsvæske tilsvarende 28 doser à 20 mikrogram (per 80 mikroliter). <u>Startpakke som inkluderer sylinderampulle og penn:</u> Pakningen inneholder 1 Terrosa sylinderampulle og 1 Terrosa penn. Styrke: 20 mikrogram/80 mikroliter MT innehaver: Gedeon Richter Plc Referanse: **Forsteo** • Injeksjonsvæske, oppløsning, ferdigfylt penn Forsteo leveres i pakningsstørrelse på 1 eller 3 penner. Hver penn inneholder 28 doser à 20 mikrogram (per 80 mikroliter). Styrke: 20 mikrogram/80 mikroliter MT innehaver: Eli Lilly	
Kommentar	Det er forskjeller i administrasjonsutstyret for Terrosa og Forsteo: Terrosa er utviklet som en penn som kan gjenbrukes med utskiftning av ampulle, mens Forsteo er en ferdigfylt penn som skal kastes etter at alle dosene er brukt opp. Klargjøring av administrasjonsutstyret er noe mer komplisert for Terrosa enn for Forsteo.	
Virkestoff (fra EPAR – European Public Assessment Report):	**<u>Teriparatid</u>** "The active substance in Terrosa, biosimilar teriparatide (also referred to as RGB-10 throughout the document), is produced in <u>E. coli</u> using recombinant DNA technology, so is the case with its reference medicinal product Forsteo."	
Kommentar produksjon	Både Terrosa og referanselegemidlet er produsert i <u>E. coli.</u>	
ATC-kode	H05AA02	
Søkegrunnlag	Artikkel 10 (4), biotilsvarende	
Kvalitativ sammensetning (fra SPC):	Biotilsvarende: **Terrosa** Iseddik Natriumacetattrihydrat Metakresol Mannitol Saltsyre (for pH-justering) Natriumhydroksid (for pH-justering) Vann til injeksjonsvæsker	Referanse: **Forsteo** Iseddik Natriumacetat (vannfri) Metakresol Mannitol Saltsyre (for pH-justering) Natriumhydroksid (for pH-justering) Vann til injeksjonsvæsker
Kommentar sammensetning	Helt lik sammensetning for biotilsvarende Terrosa som for referanselegemidlet.	

Indikasjoner (fra SPC referanseprodukt):	«FORSTEO er indisert til bruk hos voksne. Behandling av osteoporose hos postmenopausale kvinner og hos menn med økt risiko for frakturer (se pkt 5.1). Hos postmenopausale kvinner er det vist en signifikant reduksjon i forekomsten av vertebrale frakturer og ikke-vertebrale frakturer, men ikke hoftefrakturer. Behandling av osteoporose assosiert med vedvarende systemisk glukokortikoidbehandling hos kvinner og menn med økt risiko for frakturer (se pkt. 5.1).»
Biotilsvarende vurdering av kvalitet og biologisk funksjon (fra EPAR):	Quality: "The biosimilar candidate presents a rather simple, non-glycosylated structure. Extensive physicochemical, structural and biological characterisation as well as impurity profiling of both Terrosa and the reference product Forsteo has been undertaken and a high degree of similarity has been demonstrated. Head-to-head comparability data has been provided for three batches of each product, and the results support the conclusion that Terrosa can be considered biosimilar to Forsteo. The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The description of the manufacturing process and the manufacturing development is adequate. **Based on the quality data provided, Terrosa is considered to be biosimilar to Forsteo."** Biological activity "Biosimilarity regarding biological activity, was generally shown at the in vitro level, with the additional data considered as being supportive. The provided non-clinical comparability testing strategy is regarded as sufficient in the context of a biosimilar development. Applicable regulatory guidelines were taken into consideration and recommendations provided in the frame of scientific advice procedures were followed. **Comparative pharmacodynamic, pharmacokinetic and toxicology data demonstrated biosimilarity between RGB-10 (Terrosa) and the reference product Forsteo."**
Biotilsvarende vurdering av klinisk komparabilitet (PK (farmakokinetikk), PD (farmakodynamikk), effekt og sikkerhet) (fra EPAR):	"Further to the demonstration of comparability between RGB-10 and the reference medicinal product Forsteo at the analytical and the non-clinical levels, the Applicant aimed at demonstrating therapeutic equivalence of RGB-10 to Forsteo in one comparative pharmacokinetic (PK) study in 54 healthy women. The effect of teriparatide was shown to be similar across a wide range of subjects ranging from healthy volunteers and women with chronic conditions (such as hypertension, heart failure and renal impairment) to osteopenic and osteoporotic patients displaying various disease severity.

	The demonstration of clinical similarity is based on a comparative single-dose, cross-over PK study comparing single subcutaneous doses of RGB-10 (Terrosa) and Forsteo. In principle, this was considered acceptable in the particular case of a small and simple biological such as teriparatide, if the PK study showed robust evidence for comparability." "The observed difference in Cmax and AUC between RGB-10 and Forsteo likely became detectable (i.e. reached statistical significance) by an overestimation of the sample size for the first stage of the study (which is per se not a justification for the existence of a difference). Judging from available literature for Forsteo with regard to the impact of body weight and administration site on clinical outcomes, the clinical impact of the observed difference, however, was considered to be negligible. No major differences were identified by further analyzing delivered volumes, active content, structure of the active substance and the PK assay. **Therefore RGB-10 and Forsteo were considered to be similar from a pharmacological perspective."** Effektstudier: NA Safety: "The type of AEs (adverse events) reported was in line with those listed in Forsteo SmPC, mostly nausea, dizziness, headache, injection site erythema, vomiting and presyncope. Taken together it is agreed that the safety profile of Forsteo and RGB-10 can be considered comparable, and is therefore acceptable."
Vurdering av immunogenisitet fra EPAR: Fra SPC: Artikkel fra PubMed:	"No analysis of immunogenicity parameters has been performed, because a clinically relevant immunogenic potential of RGB-10 appears to be highly unlikely, as the immunogenic potential of Forsteo has proved to be negligible in the clinical studies for registration purposes as well as over the 10 years on the market. " Nevertheless the lack of clinical characterisation of the immunogenicity of RGB 10 still presents a gap in the biosimilar exercise which needs to be addressed in an appropriate way, especially as some differences between RGB-10 and Forsteo could be seen in the PK endpoints, no clinical efficacy/safety (+immunogenicity) study was conducted or is planned and the non-clinical study does not help to dispel remaining concerns. With respect to this issue, the Applicant proposed to provide the immunogenicity data of a Japanese efficacy/safety study RGB1023031 comparing RGB-10 with Forsteo (teriparatide;

	Japan). This study is ongoing and is carried out by the Japanese partner of the Applicant. The Applicant has submitted a study protocol (RGB1023O31) version 1.1 (04/03/2016) for this phase 3 clinical study: A comparative study to evaluate the similarity of RGB-10 to Forsteo in patients with osteoporosis at high risk of fracture. Forsteo: «I en stor klinisk studie ble antistoffer som kryssreagerte med teriparatid påvist i 2,8 % av kvinnene som fikk FORSTEO. Generelt ble antistoffer først påvist etter 12 måneders behandling og forsvant etter avsluttet behandling. Hypersensitivitetsreaksjoner, allergiske reaksjoner, effekt på serumkalsium eller effekt på benmineraltetthet (BMD) respons ble ikke påvist.» A multicenter, randomized, rater-blinded, parallel-group, phase 3 study to compare the efficacy, safety, and immunogenicity of biosimilar RGB-10 and reference once-daily teriparatide in patients with osteoporosis. Hagino H, Narita R, Yokoyama Y, Watanabe M, Tomomitsu M. Osteoporos Int. 2019 Oct;30(10):2027-2037: "Safety profiles, including immunogenicity, were comparable. In conclusion, the results of our study established therapeutic equivalence and comparable safety, including immunogenicity, between RGB-10 and the reference teriparatide, further substantiating the claim of biosimilarity."
Totalvurdering (fra EPAR, benefit/risk)	Benefit-risk balance For a biosimilar, the benefit-risk balance is derived from the reference product, provided the totality of evidence collected from the physicochemical and biological characterisation and the non-clinical and clinical data package supports the comparability of the two products, which CHMP considered to be the case. The overall Benefit/Risk balance of Terrosa 20 µg/80 µL solution for injection is positive.
Opptak på byttelisten i henhold til retningslinjene	Terrosa er vurdert av EMA til å være biotilsvarende med Forsteo. Komparabilitets- og funksjonelle analyser viser at teriparatid fra Terrosa og Forsteo er meget like både mht kvalitet, biologisk funksjon og klinikk, og de små forskjellene som er påvist, er vurdert til ikke å ha noen betydning for verken effekt, sikkerhet eller immunogenisitet. Kommentarer om administrasjonsutstyret: Administrasjonsutstyret er ulikt ved at Terrosa-pennen må klargjøres ved å sette inn en ampulle, mens Forsteo-pennen er ferdigfylt. Etter at ampullen er satt inn i Terrosa-pennen, er fremgangsmåten for bruk av de to legemidlene lik. Lege kan reservere pasienten mot bytte dersom det er individuelle

	medisinske forhold knyttet til pasientens situasjon som taler mot bytte, for eksempel hvis det vurderes at pasienten vil kunne ha problemer med å håndtere administrasjonsutstyret. **Konklusjon:** Legemiddelverket anbefaler opptak på byttelisten