Semglee - sammendrag av bytte

Preparat (Biotilsvarende og referanse)	**Biotilsvarende:** Semglee injeksjonsvæske, oppløsning i ferdigfylt penn 100 E/ml MT-innehaver: Viatris **Referanse:** Lantus injeksjonsvæske, oppløsning i ferdigfylt penn 100 E/ml MT-innehaver: Sanofi-Aventis	
Virkestoff	Insulin glargin	
Kommentar om virkestoff	Insulin glargin i Semglee er fremstilt ved rekombinant DNA-teknologi i *Pichia pastoris.* Insulin glargin i Lantus er fremstilt ved rekombinant DNA-teknologi i *Escherichia coli.* Aminosyresekvensen for insulin glargin i Semglee er lik som for insulin glargin i Lantus.	
ATC-kode	A10A E04	
Søkergrunnlag	Artikkel 10(4) biotilsvarende søknad	
Kvalitativ sammensetning *Identisk for referanse og biotilsvarende*	*Semglee* • Sinkklorid • Metakresol • Glyserol • Saltsyre (til pH-justering) • Natriumhydroksid (til pH-justering) • Vann til injeksjonsvæsker	*Lantus* • Sinkklorid • Metakresol • Glyserol • Natriumhydroksid (til pH-justering) • Saltsyre (til pH-justering) • Vann til injeksjonsvæsker
Indikasjon *Identisk for referanse og biotilsvarende*	Behandling av diabetes mellitus hos voksne, ungdom og barn fra 2 år og eldre.	
Farmakologiske egenskaper (Fra SPC)	**Farmakoterapeutisk gruppe:** Midler til diabetesbehandling, insulin og analoger til injeksjon, langtidsvirkende. Den primære effekt av insulin, inkludert insulin glargin, er regulering av glukosemetabolismen. Insulin og insulinanaloger senker blodsukkernivået ved å stimulere perifert glukoseopptak, særlig i skjelettmuskulatur og fettvev, og ved hemming av glukoseproduksjonen i lever. Insulin hemmer lipolyse i fettceller, hemmer proteolyse og øker proteinsyntesen. Insulin glargin er en human insulinanalog utviklet slik at den er tungt løselig ved nøytral pH. Insulin glargin foreligger oppløst ved den lave pH (pH 4) i injeksjonsoppløsningen. Den sure oppløsningen nøytraliseres etter injeksjon subkutant, og det dannes mikroutfellinger som kontinuerlig frigjør små mengder	

	insulin glargin. Dette gir en jevn, flat og forutsigbar konsentrasjons-/tidsprofil med forlenget virkningstid.
Biotilsvarende vurdering (fra EPAR): https://www.ema.europa.eu/en/documents/assessment-report/semglee-epar-public-assessment-report_en.pdf	*Kvalitet:* An extensive biosimilarity exercise was conducted to demonstrate analytical similarity of the test product MYL1501D with the reference product Lantus approved in the EU. The quality of Semglee is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Biosimilarity to the reference product Lantus has been satisfactorily demonstrated at the quality level. *Farmakokinetikk/farmakodynamikk* The Semglee clinical pharmacology programme consisted of two studies, which were single dose crossover euglycaemic clamp studies. In respect to this application study GLARGCT100111 was conducted to demonstrate definitive PD and PK similarity between Semglee and Lantus EU in T1DM subjects. The PK results support a conclusion of biosimilarity. While equivalence for PD endpoints is not formally shown*, PD results still reasonably support PK data. The data presented by the applicant in respect to analytical characterisation and non-clinical in vitro tests indicate similarity between MYL-1501D and EU-insulin glargine and results of the functional assays are reliable. Thus, similarity at the analytical and functional level together with PK similarity makes it unlikely that the variability in the PD data reflects product-related dissimilarity. Hence, GIR endpoints can be considered as secondary endpoints in line with the “Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues" *Effekt, sikkerhet og immunogenisistet* One phase III study was conducted with MYL-1501D to compare efficacy, safety and immunogenicity of MYL501D with Lantus US in patients with T1DM. As the euglycaemic clamp PK/ PD studies are considered to be the most sensitive approach in establishing similar efficacy of two insulins claimed to be biosimilar, study MYL-GAI-3001 is considered only supportive with regard to efficacy in this application dossier. In a biosimilar application, safety assessment of the test product is mainly focused on comparison to the reference product (Lantus) with respect to immunogenicity. General adverse events (AEs) and hypoglycaemia were also assessed and revealed no special safety concerns for Insulin Glargine Mylan. Immunogenicity was assessed at three levels, injection site reactions, hypersensitivity reactions and formation of anti-drug antibodies (ADAs). The latter were characterised with respect to incidence and semi-quantitative plasma level (a substitute for titre). Injection site reactions were not observed in the main phase 3 study; potential hypersensitivity reactions were infrequent and fairly balanced between the treatment groups. ADA incidences and plasma levels were similar between the Glargine Mylan and Lantus group. Thus, there was no hint for increased immunogenicity of Glargine Mylan from these observations.

	Toksikologi: According to the current version of the European biosimilar guideline, toxicology studies are not necessary for a biosimilar application unless there is cause for concern. In the case of Mylan's insulin glargine, it should be noted that it is produced in Pichia yeast, whereas the reference product is produced in E. coli, leading to low levels of glycosylated species in the test product vs. no glycosylated species in the reference product. However, the applicant achieved a reduction of the glycosylated forms to very low levels so that the potential toxicological impact of the glycosylated forms in Mylan's glargine is considered negligible. The most relevant repeat-dose study in rats (G11066), comparing a recent Mylan formulation with EU- and US-Lantus, revealed no toxicological concerns. *Inspection of the blinded to sequence (but not blinded to subject ID) PD data, revealed a number of profiles which had no glucose infusion requirements during a clamp period. In these cases, AUCGIR.0-30h and GIRmax are equal to zero and no log-transformation is possible. In addition, several subjects had very low glucose infusion requirements. Therefore, it was decided in the first Database Release Meeting that all subjects with any profiles of AUCGIR.0-30h ≤ 50 (h*mg/kg/min) should be excluded from the primary PD analysis.
Totalvurdering (fra EPAR; benefit/risk)	Considering the totality of data from the comparability exercise, biosimilarity of Semglee to the comparator Lantus was shown. No risks of Semglee beyond the known effects of insulin glargine were detected. In line with the biosimilar insulin guideline, extrapolation to intravenous use and all indications and age groups of the reference medicinal product is acceptable.
Opptak på byttelisten i henhold til retningslinjene	Semglee er vurdert av EMA til å være biotilsvarende med Lantus. Biotilsvarenhet er vist mhp. kvalitet, biologisk funksjon, farmakologiske parametere, effekt, sikkerhet og immunogenisitet. Kommentarer om administrasjonsutstyret: De ferdigfylte pennene er vurdert som bruksmessig likeverdige av Byttegruppen. Det er ulik farge på pennene (blå/grå), men Byttegruppen mener at dette ikke er til hinder for at legemidlene kan byttes i apotek. Lege kan reservere pasienten mot bytte dersom det er individuelle medisinske forhold knyttet til pasientens situasjon som taler mot det. **Konklusjon: Legemiddelverket anbefaler opptak på byttelisten**