Vurdering av byttbarhet – Insulin lispro Sanofi og Humalog

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| **Preparat** (biotilsvarende og referanse)<br><br>(Fra SPC): | Biotilsvarende: **Insulin lispro Sanofi**<br>• Injeksjonsvæske, oppløsning i ferdigfylt penn<br><br>Hver ferdigfylte penn inneholder 3 ml, tilsvarende 300 enheter insulin lispro. Hver ferdigfylte penn gir 1-80 enheter i trinn på 1 enhet.<br><br>Styrke: 100 enheter/ml<br>MT innehaver: Sanofi<br><br>Referanseprodukt: **Humalog**<br>• KwikPen injeksjonsvæske, oppløsning i ferdigfylt penn<br><br>Hver ferdigfylte penn inneholder 300 enheter insulin lispro i 3 ml oppløsning. Hver ferdigfylte penn leverer 1-60 enheter i trinn på 1 enhet.<br><br>Styrke: 100 enheter/ml<br>MT innehaver: Eli Lilly | |
| **Kommentar** | Byttegruppen anser administrasjonsutstyret som likeverdig, med unntak for fargen på injeksjonspennene. | |
| **Virkestoff**<br>(Fra EPAR (European Public Assessment Report)): | **Insulin lispro**<br>«Insulin lispro Sanofi is an insulin lispro, an analogue protein of human insulin. It is a genetically engineered recombinant protein produced in Escherichia coli cells. Insulin lispro belongs to the pharmacotherapeutic group: drugs used in diabetes, insulins and analogues for injection, fast-acting." | |
| **Kommentar produksjon** | Både Humalog og referanselegemidlet er produsert i E. coli. | |
| **ATC-kode** | A10A B04 | |
| **Søkegrunnlag** | 10(4), biotilsvarende | |
| **Kvalitativ sammensetning** | Biotilsvarende: **Insulin lispro Sanofi**<br>Metakresol<br>Glyserol<br>Dinatriumhydrogenfosfathepta-hydrat<br>Sinkoksid<br>Vann til injeksjonsvæsker<br>Saltsyre (til pH-justering)<br>Natriumhydroksid (til pH-justering) | Referanse: **Humalog**<br>m-Kresol<br>Glyserol<br>Dinatriumfosfatheptahydrat<br>Sinkoksid<br>Vann til injeksjonsvæsker<br>Saltsyre (til pH-justering)<br>Natriumhydroksid (til pH-justering) |
| **Kommentarer sammensetning** | Helt lik sammensetning for biotilsvarende som for referanselegemidlet. | |
| **Indikasjon** (fra SPC): | «Til behandling av voksne og barn med diabetes mellitus som trenger insulin for å opprettholde normal glukosehomeostase. Insulin lispro Sanofi er også indisert til initiell stabilisering av diabetes mellitus.» | |
| **Biotilsvarende vurdering av kvalitet og biologisk funksjon** (fra EPAR): | Quality<br>"The composition of the biosimilar is comparable to the reference product. Analytical data of Humalog batches regarding these parameters have been submitted. The results support that Insulin lispro Sanofi is similar to Humalog with regard to the composition. The applicant has performed an extensive biosimilarity study. A considerable number of batches have been analysed in the study, and Insulin lispro Sanofi was compared to both EU and US | |

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| | Humalog products. The comparability exercise covered similarity between Insulin lispro Sanofi and the reference product and demonstrated that Humalog US can be considered representative of Humalog EU.<br>The overall quality documentation provided in the Insulin lispro Sanofi marketing authorization application is of adequate quality and support biosimilarity to the reference product Humalog. In conclusion, based on the review of the quality data provided, the marketing authorisation application for Insulin lispro Sanofi is approvable from the quality point of view."<br>Biological activity<br>The applicant has performed all pharmacodynamic tests which are required to demonstrate biosimilarity at the non-clinical level, evaluating the receptor binding and activation, and metabolic activity characteristics of SAR342434 (insulin lispro Sanofi) and Humalog. In addition, activation of the IGF-1 receptor and effect on tumour cell proliferation was also investigated. All experiments were conducted in vitro, in line with the requirements of the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1).<br>Based on the results submitted, Insulin lispro Sanofi can be considered similar to the reference product Humalog in terms of in vitro functionality and toxicological, toxicokinetic and local tolerance profiles. |
| **Biotilsvarende vurdering av klinikk** (PK (farmakokinetikk), PD (farmakodynamikk), effekt og sikkerhet)<br><br>(Fra EPAR): | Pharmacokinetics:<br>"Mean plasma concentration vs. time curves of SAR342434* and Humalog EU were comparable. The treatment ratios and 90% CIs for PK parameters were calculated in accordance with the statistical analysis plan and using acceptable methodology, and pre-defined biosimilar comparability limits (0.80 to 1.25) are acceptable.<br>The point estimates [90% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PK-parameters INS-Cmax and INS-AUClast were 0.96 [0.89 to 1.04] and 0.97 [0.94 to 1.01], respectively. The results indicate similar pharmacokinetics between SAR342434 vs. Humalog EU. The results for secondary PK endpoints support this conclusion.<br><br>*insulin lispro Sanofi<br><br>Pharmacodynamics:<br>"The variability of blood glucose level during the clamp* was acceptable.<br>The point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU for the primary PD parameters GIR*-AUC0-12h and GIRmax were 1.06 [0.95 to 1.17] and 1.07 [0.98 to 1.16], respectively. The results indicate similar pharmacodynamic effect between SAR342434 vs. Humalog EU. In addition, similar pharmacodynamics effect between SAR342434 vs. Humalog US was demonstrated for the primary PD parameters. |

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| | Regarding secondary PD endpoints, the point estimates [95% CIs] of treatment ratio for SAR342434 vs. Humalog EU 95% were 1.13 [0.99-1.29] and 0.94 [0.68-1.31] for GIR-AUC0-2 and GIR-AUC4-12, respectively, i.e. outside the equivalence margin (0.80 to 1.25). However, this was not considered to negatively impact on the similarity comparability, as the primary PD endpoints for rapid- and shortacting insulins as defined in Guideline EMEA/CHMP/BMWP/32775/2005_Rev. 1, demonstrated similar pharmacodynamic effect between SAR342434 (insulin lispro Sanofi) and Humalog EU.<br>Regarding efficacy, the evaluation of HbA1c is not a sensitive endpoint and therefore efficacy studies evaluating HbA1c are not requested (EMEA/CHMP/BMWP/32775/2005_Rev. 1)."<br><br>* Euglycaemic clamp technique<br>*Body weight standardised glucose infusion rate<br><br>Safety:<br>"No relevant differences were observed between SAR342434 and Humalog in patients with any AEs (adverse events), TEAEs (Treatment-emergent adverse events), treatment emergent SAEs (Serious adverse event), TEAEs leading to death or TEAEs leading to permanent IMP discontinuation. The size of the safety database and duration of exposure is considered appropriate for the evaluation of the general safety profile of Insulin lispro Sanofi. Safety and tolerability of Insulin lispro Sanofi and Humalog seem to be comparable and thus support biosimilarity of these two products." |
| **Vurdering av immunogenisitet** (fra EPAR): | "With regard to immunogenicity, the differences in the anti-drug antibody (ADA) response between SARS342434 and Humalog were small and inconsistent. Treatment-emergent ADA did not affect efficacy or safety endpoints in either T1DM (type1 diabetes mellitus) or T2DM (type 2 DM) subjects. In conclusion, the safety profile of Insulin lispro Sanofi is acceptable and not different to that of Humalog." |
| **Totalvurdering** (fra EPAR, benefit/risk) | As biosimilarity in terms of quality, non-clinical, clinical PK and PD, safety and efficacy has been demonstrated, the benefit-risk balance for Insulin lispro Sanofi is considered positive. |
| **Opptak på byttelisten i henhold til retningslinjene** | Insulin lispro Sanofi er vurdert av EMA til å være biotilsvarende med Humalog. Komparabilitets- og funksjonelle analyser viser at Insulin lispro Sanofi og Humalog er meget like både mht kvalitet, biologisk funksjon og klinikk (PK/PD), og de små forskjellene som er påvist, er vurdert til ikke å ha noen betydning verken for effekt, sikkerhet eller immunogenisitet.<br><br>Kommentarer om administrasjonsutstyret:<br>Bruksmessig er pennene vurdert som likeverdig av Byttegruppen. Det er forskjellig farge på insulinpennene, noe som kan være utfordrende for enkelte pasientgrupper. Lege kan reservere pasienten mot bytte dersom det er individuelle medisinske forhold knyttet til pasientens situasjon som taler mot bytte. |

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| | **Konklusjon:** Legemiddelverket anbefaler opptak på byttelisten. |