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(54) Title: LONG-ACTING INSULIN ANALOGUE PREPARATIONS IN SOLUBLE AND CRYSTALLINE FORMS

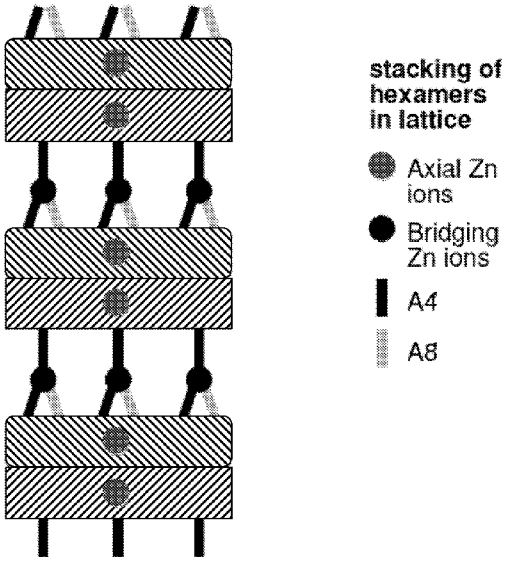


FIG. 1F

(57) Abstract: A pharmaceutical formulation comprises an insulin analogue or a physiologically acceptable salt thereof, wherein the insulin analogue or a physiologically acceptable salt thereof contains an insulin A-chain sequence that contains paired Histidine substitutions at A4 and A8, and optionally a substitution at A21. The formulation further contains a pharmaceutically acceptable buffer containing at least about 4 zinc ions per 6 insulin analogue molecules. The formulation forms a long-acting zinc-dependent subcutaneous depot upon subcutaneous injection. In a zinc-free formulation, the insulin analogue monomer exhibits decreased affinity for the Insulin-like Growth Factor receptor and at least 20% of the affinity for the insulin receptor of the same species, in comparison to an otherwise identical insulin or insulin analogue that does not contain the His^{A4} and His^{A8} substitutions.

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