FACT SHEET

Insulin

Key words

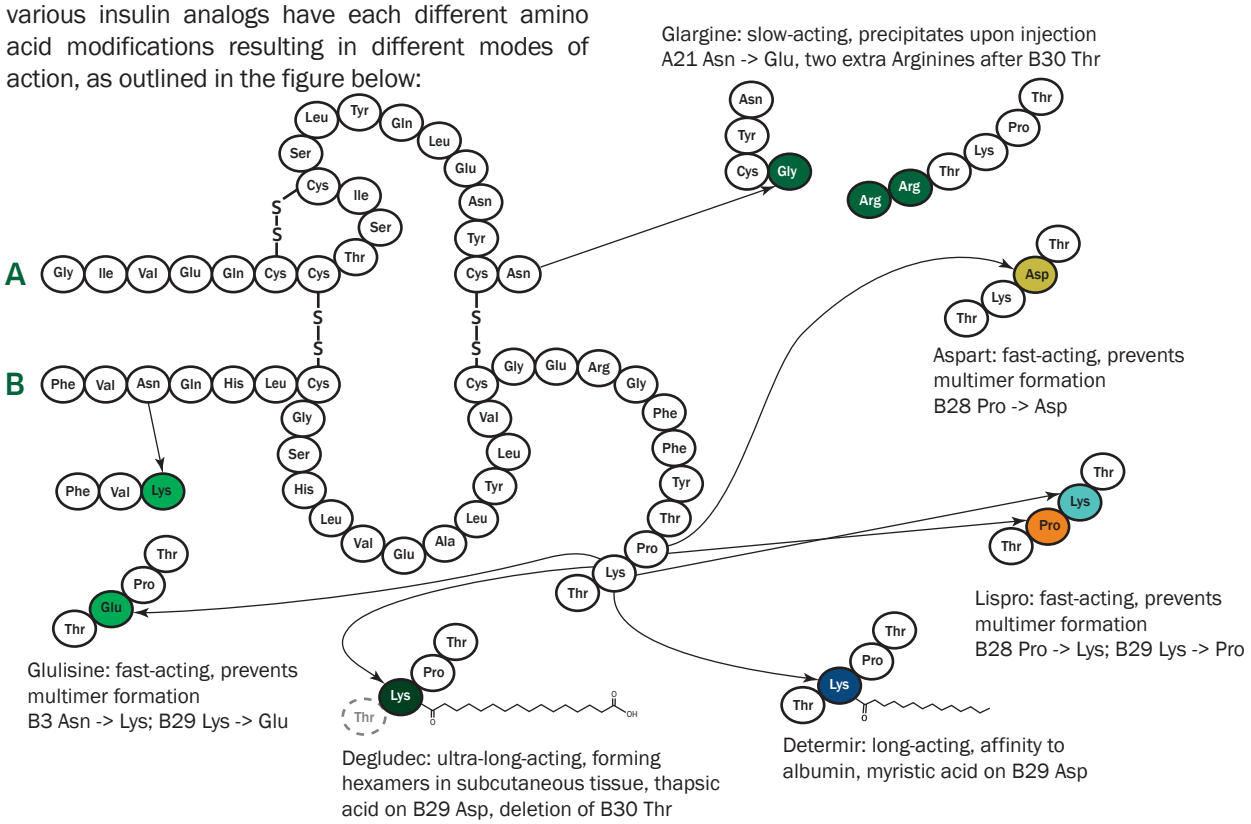
- Drug class: peptide hormone
- Molecule: a heterodimer of two short peptides linked by disulfide bridges
- Binding/inhibiting/MoA: binds IR-A and IR-B receptors to open GLUT-4 glucose transporter
- Originator brand name: depending on variant

Molecule

Animal-sourced insulins are now rarely available in developed countries, and even the use of recombinant human insulin is declining in different markets, whereas insulin analogs are dominating the market for years. Basal insulins are long-acting, and bolus insulins are fast-acting. Action length can also be influenced by the formulation, e.g. isophane insulin.

Mode of Action

Insulin opens the glucose transporter GLUT-4 to import glucose into the cells and further influences glycogen synthesis and adiposynthesis to store it. The various insulin analogs have each different amino acid modifications resulting in different modes of action, as outlined in the figure below:



Indication

Insulin is indicated to treat high blood glucose, including diabetes mellitus type 1 and 2, gestational diabetes, and complications of diabetes such as diabetic ketoacidosis and hyperosmolar hyperglycemic states. Insulin is also used with glucose to treat high blood potassium levels. Depending on the disease type and stage, different insulin analogs or mixtures thereof are prescribed.

Patent Situation

Patent protection of recombinant human insulin has expired for more than 15 years and also patents for many analogs have expired so far, e.g., for Lantus® and Humalog®.

Market and Competitive Field

The originator product of insulin lispro, Eli Lilly's Humalog®, was approved in 1996 by FDA and EMA as the first insulin analog. In 2023, global sales of Humalog® were 1.56 bn €. Sanofi-Aventis' Lantus® (insulin glargine) had a turnover of 1.42 bn €. A steady decline in the originator market share indicates a high potential for biosimilar products.

v Installed at VelaLabs under GxP ○ Analytical concept exists/installed under R&D

Insulin and Insulin variants: selected GMP, GLP, GCLP methods

Characterisation of the molecule & GxP techniques

CBA - CELL BASED ASSAYS

- v Inculin receptor autophosphorylation reporter gene assay
- v Glucose transport
- v Glycogen formation
- v Attenuation of gluconeogenesis
- v Lipogenesis
- v Inhibition of lipolysis
- v Metabolic assay

LBA - LIGAND BINDING ASSAYS

- v Insulin receptor A binding affinity
- v Insulin receptor B binding affinity
- v Affinity to IGF-1R

(PRE-) CLINICAL ANALYTICS under G(C)LP

- ○ PD - Pharmacodynamics
- ○ PK - Pharmacokinetics
- ○ ADA - Anti-Drug Antibody testing
- ○ Biomarker studies

PCM - PHYSICOCHEMICAL ASSAYS

- ○ Size exclusion HPLC
- ○ Ion exchange HPLC
- ○ Reversed phase HPLC
- ○ Desamido A21 determination
- ○ Glycerol determination
- ○ Phenol determination (isophane suspension)
- ○ Capillary electrophoresis
- ○ cIEF (capillary isoelectric focusing)

COMPENDIAL PCM METHODS (EP & USP)

- ○ pH measurement (EP 2.2.3)
- ○ Appearance (EP 2.2.1)
- ○ Turbidity (EP 2.2.1)
- ○ Colour of solution (EP 2.2.2)
- ○ Osmolality (EP 2.2.35)
- ○ Visible particles (2.9.20)
- ○ Subvisible particles (2.9.19)
- ○ Extractable volume (EP 2.9.17)
- ○ Protein concentration by OD280 (EP 2.5.33)
- ○ Zinc determination (within Tentamus Group)

MICROBIOLOGY / SAFETY

- v Sterility (EP 2.6.1)
- v Endotoxin, gel-clot limit test (EP 2.6.14)
- v Endotoxin, chromogenic LAL test (EP 2.6.14)
- v Endotoxin, recombinant Factor C (EP 2.6.32)

* The European Pharmacopeial has no dedicated chapters for different injectable formulations. USP or BP monographs can be used instead