

## Insulin – Fact Sheet

### Molecule

Animal sourced insulins are now rarely available in developed countries and even use of recombinant human insulin is declining in different markets whereas insulin analogues are dominating the market since years. Basal insulins are long acting, bolus insulins are fast acting.

### Mode of Action

The various insulin analogues have each different amino acid modifications resulting into different Mode of Actions as presented in the table below.

Insulin analogue	Modification	Molecular weight	Mode-of-action
Insulin lispro	Proline B28 replaced by lysine and lysine B29 replaced by proline	58.1 kDa	Fast acting, blocking of multimers
Insulin aspart	Proline B28 replaced with aspartic acid	58.3 kDa	Fast acting, blocking of multimers
Insulin glulisine	Asparagine B3 replaced by lysine and lysine B29 replaced by glutamic acid	58.2 kDa	Fast acting, blocking of multimers
Insulin glargine	Asparagine N21 replaced by glycine and two arginines added to carboxy terminus of B chain	60.6 kDa	Long acting, initial precipitation and delayed absorption
Insulin detemir	A special fatty acid - myristic acid bound to lysine B29	59.1 kDa	Long acting, affinity for albumin
Insulin degludec	Threonine B30 deleted, at lysine B29 conjugated to hexadecanedioic acid via gamma-L-glutamyl spacer	61.0 kDa	Ultra-long acting, formation of multi-hexamers in subcutaneous tissues

### 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 analogues 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 analogues have been 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 analogue. In 2019, global sales of Humalog® were 2.76 billion €. Sanofi-Aventis's Lantus® (insulin glargine) had a turnover of 1.95 billion €.

<b>Insulin Analogues</b>	Humalog®, NovoLog®, NovoRapid®, Apidra®, Lantus®, Levemir®, Tresiba®
<b>Biosimilars</b>	Basalog®, Basaglar™, Abasaglar™, Basalin®, Prandilin®, Lisduna™, Semglee™
<b>Assays</b>	
<b>Receptor binding</b>	
Affinity of insulin to insulin receptor A and B – kinetics (Biacore)	
<b>Receptor auto-phosphorylation</b>	
Bioassay measuring receptor auto-phosphorylation	Not required
<b>Metabolic activity</b>	
Glucose transport (uptake in 3T3-L1 cells)	
Lipogenesis (bioassay quantifying free fatty acids after insulin treatment)	
Glycogen formation (bioassay quantifying glycogen after insulin treatment)	
<b>Mitogenic activity</b>	
Insulin dependent mitogenic activity (bioassay based on SAOS-2 cells)	
<b>Batch release EU</b>	

