Insulin Type

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Insulin

Insulin has been commercially available since the early 1920s and is arguably the best studied form of therapy for diabetes. It is essential for all patients with T1DM and a mainstay of treatment for T2DM.

Insulins are grouped into **shorter-acting** versus **longer-acting** formulations.

Both shor-tacting and long-acting insulins have profiles of action that vary by the size of the dose injected.

With higher doses the onset and time to peak effect become more delayed and the total duration longer.

Types and Generic Names (Commercial Names)	Onset of Action (Minutes)	Time to Peak (Hours)	Duration (Hours)	Administration
Rapid Acting				
Aspart (Fiasp)	<5	0.5–1.5	3–5	Just before or just after meals
Aspart (Novolog)	10–20	0.5–1.5	3–5	0–15 minutes before or just after meals
Lispro (Humalog)	10–20	0.5–1.5	3–5	
Glulisine (Apidra)	10–20	0.5–1.5	3–5	
Short Acting				
Regular human (Humulin R, Novolin R)	30–45	2–4	4–8	15-30 minutes before meals
Intermediate Acting				
NPH (Humulin N, Novolin N)	60–120	4–8	12–20	Once or twice daily

Types and Generic Names (Commercial Names)	Onset of Action (Minutes)	Time to Peak (Hours)	Duration (Hours)	Administration
Long Acting				
Detemir (Levemir)	60–120	6–10	16–24	Usually once daily
Glargine (Lantus, Basaglar)	60–120	No pronounced peak	~24	
Degludec (Tresiba)	60–120	No pronounced peak	Up to 72	
Premixed				
70/30 NPH/R (Humulin 70/30, Novolin 70/30)	30–40	4–8	12–20	Usually twice daily, 0–30 minutes before meals
75/25 Protamine-lispro/lispro (Humalog Mix 70/30)	10–20	4–8	12–20	
70/30 Protamine-aspart/aspart (Novolog Mix 70/30)	10–20	4–8	12–20	
50/50 Protamine-lispro/lispro (Humalog Mix 50/50)	10–20	4–8	12–20	
50/50 Protamine-aspart/aspart (Novolog Mix 50/50)	15–60	4–8	12–20	
Concentrated				
U-500 human regular (Humulin U-500)	30–45	6–12	12–24	Twice daily
U-200 degludec (Tresiba U-200)	60–120	No pronounced peak	>24	Once daily
U-300 glargine (Toujeo 300 U/mL)	60–120	No pronounced peak	Up to 72	Once daily

Glucose Factors Contributing to A1C

A1C =

Factors contributing to the fasting glucose level:

- Hepatic glucose production
- Hepatic insulin resistance

+

Factors contributing to the postprandial glucose level:

- Preprandial glucose level
- Insulin secretory capacity
- Glucose load from meal
- Insulin sensitivity of the peripheral tissues

Joslin Diabetes Center

Long-acting insulins are usually initiated before short-acting ones.
In the past, formulations of human insulin were modified to prolong its action by slowing absorption

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units or 0.1–0.2 units/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent. While there is evidence for reduced risk of hypoglycemia with newer, longer-acting, basal insulin analogs, people with type 2 diabetes without history of hypoglycemia or severe hypoglycemia may use NPH safely at much lower cost

The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals.

Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog.

rationale for starting with basal insulin replacement

- Simple
  - One injection a day
    - Start 10 to 20 units at bedtime and adjust based on fasting blood glucose (FBG)
  - Self-adjustment of insulin dose
- Effective
  - A1C reduction of 1.0% to 2.5%
- Safe
  - Lower risk of hypoglycemia (esp. nocturnal)
- Less weight gain

NPH human insulin is still commonly used. The time to onset, peak effect, and full duration of action of NPH are about twofold greater than those of regular human insulin, with an onset in 1 to 2 hours, a peak usually at 4 to 8 hours, and a duration of 12 to 16 hours.

Insulin **Detemir** is a long-acting analogue in which a fatty acid side chain is covalently bound to the insulin molecule, resulting in slowing of both absorption from subcutaneous tissue and clearance from circulation.

Detemir's time of onset and duration of action are quite similar to those of NPH, but more consistent from injection to injection.

To reliably provide a sustained between-meal and overnight (basal) effect, both NPH and detemir must be taken twice daily, usually before breakfast and either before dinner or at bedtime.

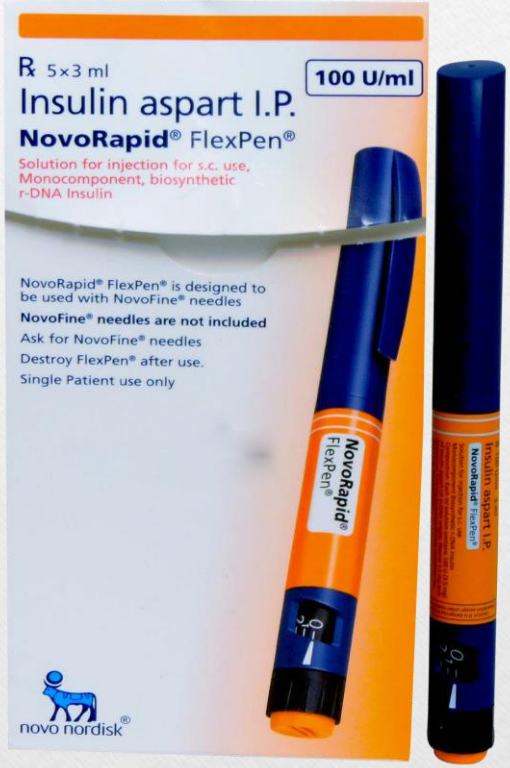
Insulin **Glargine** is a long-acting analogue that is soluble at acid pH but precipitates when neutralized in tissues after injection.

The resulting gradual absorption leads to a duration of action that, at doses commonly needed in T2DM, usually provides more than 24 hours of basal insulin effect with relatively little peak to trough variation.

Insulin **Degludec** and a more concentrated formulation (300 units/mL) of insulin glargine have recently been introduced, and both provide even longer and flatter profiles of action than detemir and glargine.

The pharmacokinetics of these newer long-acting insulins result in even lower risk of hypoglycemia than with glargine, but their advantage over glargine in this respect appears smaller than that with glargine versus NPH

NOVORAPID


℞ 5×3 ml
100 U/ml
Insulin aspart I.P.
NovoRapid® FlexPen®
Solution for injection for s.c. use,
Monocomponent, biosynthetic
r-DNA Insulin
NovoRapid® FlexPen® is designed to
be used with NovoFine® needles
NovoFine® needles are not included
Ask for NovoFine® needles
Destroy FlexPen® after use.
Single Patient use only
novo nordisk®
NovoRapid®
FlexPen®
Insulin aspart I.P.
NovoRapid® FlexPen®

NOVOMIX

Rx PRESCRIPTION DRUG
NovoMix® 30
FlexPen®
100 U/ml 5×3 ml
Suspension for injection in a pre-filled pen
Insulin aspart
Subcutaneous use
NovoMix® 30 FlexPen® is designed to be used with NovoFine® needles
NovoFine® needles are not included
NovoMix® 30
FlexPen®

APIDRA

Apidra® SoloStar®
100 Unités/ml - 100 Units/ml
Insuline glulisine / Insulin glulisine
Voie sous-cutanée
Subcutaneous use
Solution injectable en stylo prérempli
Solution for injection in a pre-filled pen
5 stylos de 3 ml /5 pens of 3 ml
sanofi aventis

Apidra® SoloStar®
100 Unités/ml - 100 Units/ml
Insuline glulisine/Insulin glulisine

LISPRO

Humalog® Mix50™
100 U/ml
KwikPen™
5 x 3 ml pre-filled pens
Subcutaneous use
Humalog® Mix25™
100 U/ml
KwikPen™
5 x 3 ml pre-filled pens
Subcutaneous use
Humalog®
100 U/ml
KwikPen™
5 x 3 ml pre-filled pens

LANTUS

Lantus® SoloStar®
100 Unités/ml - 100 Units/ml
Solution injectable en stylo prérempli
Solution for injection in a pre-filled pen
insuline glargine / insulin glargine
Voie sous-cutanée / Subcutaneous use
5 stylos de 3 ml / 5 pens of 3 ml
sanofi aventis
Lantus® SoloStar®
100 Unités/ml - 100 Units/ml

LEVEMIR

DEGLUDEC

Recombinant DNA origin
5×3 mL pre-filled pen
Insulin Degludec
Tresiba®
FlexTouch®
100 units/ml
Solution for injection
Solution for injection in pre-filled pen
For subcutaneous use
Manufactured by
Novo Nordisk A/S
Novo Alle
DK-2880 Bagsværd, Denmark
Imported and Distributed by
Novo Nordisk Pharmaceuticals (Philippines) Inc.
Unit 2006 One San Miguel Avenue Bldg.
San Miguel Ave. cor. Shaw Blvd.
Ortigas Center, Pasig City 1605
Philippines
Rx
novo nordisk
Insulin Degludec
Tresiba

TOUJEO

Toujeo® SoloStar®
300 units/ml
solution for injection in a pre-filled pen
insulin glARGine
Subcutaneous use
5 pens
SANOFI
Use only in this pen
or severe overdose
can result.
Toujeo® SoloStar®
300 units/ml injection
insulin glARGine

Short-Acting Insulins

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets.

A dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy.

Short-Acting Insulins

Ideally, these agents should be administered with a lag time before eating that is proportional to the preprandial glucose level.

The higher the glucose level, the greater amount of time before the meal the insulin should be administered to allow for onset of effect and a downward trend of premeal hyperglycemia before eating.

Short-Acting Insulins

Rapid-acting insulin should be administered earlier (e.g., 10-15 minutes before the meal) for meals that contain primarily rapidly absorbed carbohydrates to ensure onset during carbohydrate absorption. Conversely, this insulin could be administered later (e.g., at the first bite or 15 minutes after the meal) for meals with high fat content, which may slow carbohydrate absorption..

Regular insulin has an onset of action about 30 minutes after injection, a peak at 2 to 4 hours, and duration of 6 to 8 hours or longer at high doses.

The three rapid-acting analogues all have an onset in 5 to 15 minutes, peak activity in approximately 1hour, and duration of approximately 4 hours.

Premixed Insulins

Premixed insulin formulations provide greater convenience and accuracy of dosing than mixing of two formulations in a syringe by the patient at the time of administration, but at the expense of reduced flexibility of dosing

Insulin Therapy:
Indications for Basal-Bolus Treatment

- Significant insulinopenia
- Instability of glucose patterns (usually the result of significant insulinopenia)
- Difficulty with hypoglycemia
- Lifestyle needs
- Achieving therapeutic goals
- Weight loss

Clinical Features of Commonly Used Injectable Agents Other Than Insulin

Types and Generic Names (Commercial Names)	Administration	Main Effects	Contraindications	Side Effects
Short-acting GLP1 agonist				
Exenatide (Byetta)	5–10 μg BID before breakfast and dinner	Postprandial glucose control and weight loss	T1D DKA Pancreatitis History medullary carcinoma	Nausea, diarrhea, abdominal pain Pancreatitis?
Lixisenatide (Adlyxin)	10–20 μg QD before breakfast			
Long-acting GLP1 agonist				
Liraglutide (Victoza)	0.6–1.8 mg daily	Basal glucose control and weight loss	T1D DKA Pancreatitis History medullary carcinoma	Nausea, diarrhea, abdominal pain Pancreatitis?
Dulaglutide (Trulicity)	0.75 or 1.5 mg weekly			
Extended-release exenatide (Bydureon)	2 mg weekly			
Semaglutide (Ozempic)	0.5 or 1 mg weekly			

Clinical Features of Commonly Used Injectable Agents Other Than Insulin

Types and Generic Names (Commercial Names)	Administration	Main Effects	Contraindications	Side Effects
Fixed-dose GLP1/insulin combination				
Liraglutide/degludec (Xultophy)	Daily, titrated	Glucose and weight control	T1D DKA Pancreatitis History medullary carcinoma	Hypoglycemia Nausea, diarrhea, abdominal pain Pancreatitis?
Lixisenatide/glargine (Soliqua)	Daily before breakfast, titrated			
Amylin agonist Pramlintide (Symlin)	TID before meals in T1D or T2D requiring prandial insulin	Postprandial glucose control and weight loss	Confirmed gastro-paresis	Nausea Abdominal pain Hypoglycemia

GLP1 Receptor Agonists

Like GLP1 itself, it potentiates insulin secretion in response to rising glucose levels, suppresses postprandial glucagon secretion, delays gastric emptying and promotes satiety.

Short-Acting GLP1 Agonists

With twice-daily injection before breakfast and before dinner it produces a reduction of approximately 1% in HbA1c, largely through a reduction of postprandial glucose along with modest Weight loss 2-4 K

Long-Acting GLP1 Agonists

Long-Acting GLP1 Agonists Newer, longer-acting GLP1 receptor agonists include liraglutide, an extended-release formulation of exenatide, dulaglutide, and semaglutide.

Liraglutide is administered once daily without any restriction as to timing or relation to meals. The other long-acting agents are to be given once weekly.

In general, they are associated with greater HbA1c-lowering efficacy than short-Acting exenatide and lixisenatide, owing to their greater effects on overnight fasting glucose levels.

However, they have much Less effect on postprandial increments of glucose than the short-acting agents. They also are associated with a lower frequency of gastrointestinal side effects

Weight loss is consistently seen and similar among the various GLP1 receptor agonists, although only liraglutide is currently approved for weight loss in patients with or without diabetes

large randomized trials examining cardiovascular safety of two long-acting GLP1 agonists—liraglutide and semaglutide—have shown significant cardiovascular benefit in populations selected for having high cardiovascular risk

Results (LEADER) study followed patients randomized to treatment with liraglutide or placebo for a median of more than 3years.

Significant reductions of risk were found for the primary composite cardiovascular endpoint(13%), cardiovascular death(22%), all-cause mortality (15%), and progression of albuminuria (26%).

The Trial (SUSTAIN-6) had a generally similar design but studied patients starting with somewhat worse glycemic control who received randomized treatment for about 2 years.

This study demonstrated somewhat greater reduction of risk for its primary cardiovascular composite endpoint (26%) compared with LEADER and showed a reduction of renal endpoints. However, no reduction of mortality was found.

Treatment Effects of Liraglutide and Semaglutide in the LEADER and SUSTAIN-6 Studies

Endpoints	LIRAGLUTIDE IN LEADER		SEMAGLUTIDE IN SUSTAIN-6	
	Hazard Ratio (95% CI)	*p* Value	Hazard Ratio (95% CI)	*p* Value
Primary cardiovascular composite Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	0.87 (0.78–0.97)	0.01	0.74 (0.58–0.94)	0.02
Cardiovascular death	0.78 (0.66–0.93)	0.007	0.98 (0.65–1.48)	0.92
All cause death	0.85 (0.74–0.97)	0.02	1.05 (0.74–1.5)	0.79
Hospitalization for heart failure	0.87 (0.73–1.05)	0.14	1.11 (0.77–1.61)	0.57
Progression of albuminuria	0.74 (0.60–0.91)	0.004	NA	NA

LIRAGLUTIDE

LIRAGLUTIDE

Amylin Receptor Agonists

Amylin is a neuroendocrine hormone that is co-secreted with insulin by pancreatic beta cells. A deficiency of amylin is therefore evident in patients with T1DM or T2DM, in parallel with insulin deficiency.

Amylin and insulin have complementary Actions in regulating plasma glucose. Amylin binds to brain nuclei and promotes satiety and reduces appetite. Through efferent neural path ways it mediates a decrease in the rate of gastric emptying and limits inappropriate glucagon secretion in glucose dependent fashion.

Pramlintide was developed as a soluble, nonaggregating amylin analogue, with similar clinical effects, that is administered by injection before meals.

It is approved for use by patients with T1DM or T2DM requiring both basal and mealtime insulin. Most of the effect on glycemic patterns is a reduction of postprandial increments, with little effect on overnight control.