Pharmacology of Diabetes Medications

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American Diabetes Association®

Estimates of Diabetes and Its Burden on the US

CDC National Diabetes Statistics Report, 2014

- 9.3% (29.1 million) of the US Population have diabetes.
- Treatment of DM in people ≥ 18 years old:
  - 14% use insulin only
  - 14.7% use both insulin and oral medication
  - 56.9% use oral medication only
  - 14.4% Neither insulin nor oral medication
- 282,000 ER visits had hypoglycemia as the first diagnosis and DM as other.
- 175,000 ER visits with hyperglycemia crisis (DKA or HHS) as the first diagnosis.

https://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Estimates of Diabetes and Its Burden on the US

CDC National Diabetes Statistics Report, 2014

- 71% had BP $\geq$ 140/90 mmHg or used Rx medications for treating HBP.
- 65% had LDL $\geq$ 100 mg/dL.
- Hospitalization rates for MI were 1.8 times higher and stroke, 1.5 times higher.
- 4.2 million had diabetic retinopathy.
- 44% of kidney failure patients had DM listed as the primary cause.
- 60% of non-traumatic lower-limb amputations occurred in people with diagnosed diabetes.

https://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Standards of Medical Care in Diabetes - 2017

1. Promoting Health and Reducing Disparities in Populations
2. Classification and Diagnosis of Diabetes
3. Comprehensive Medical Evaluation and Assessment of Comorbidities
4. Lifestyle Management
5. Prevention or Delay of Type 2 Diabetes
6. Glycemic Targets
7. Obesity Management for the Treatment of Type 2 Diabetes
8. Pharmacologic Approaches to Glycemic Treatment

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Standards of Medical Care in Diabetes - 2017

9. Cardiovascular Disease and Risk Management
10. Microvascular Complications (specifically neuropathy) and Foot Care
11. Older Adults
12. Children & Adolescents
13. Management of Diabetes in Pregnancy
14. Diabetes Carein the Hospital
15. Diabetes Advocacy
16. Helpful Resources

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Learning Objectives

1. Describe the 2017 ADA recommended Pharmacologic Therapy for T1DM and T2DM.
2. Describe the mechanism of action for oral and injectable antihyperglycemic medications.
3. Compare and contrast the onset of action, peak and duration for insulins on the US market.
4. Describe pharmacologic recommendations for hypertension, lipid management and the role of antiplatelette therapy in patients with diabetes mellitus.

When your blood sugar is low..

And someone tells you to take some insulin..

Type 2 Oral Medications

- **Drug Class:** Biguanide
- **MOA:** Lowers both basal and postprandial glucose by decreasing hepatic glucose production and intestinal absorption, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
- **Generic (Brand) Name:** Metformin (Glucophage); Metformin ER (Glumetza, Fortamet)
- **Generic Available:** YES

Type 2 Oral Medications

MOA: Stimulates insulin secretion from functioning beta cells in the pancreas, particularly in response to a meal.

- **Drug Class**: Sulphonylureas
- **Generic (Brand) Name:** Glimepiride (Amaryl); Glipizide (Glucotrol, Glucotrol XL); Glyburide, glibenclamide (Micronase, Glynase, Diabeta)
- **Generic Available:** YES

- **Drug Class:** Meglitinides
- **Generic (Brand) Name:** Nateglinide (Starlix); Repaglinide (Prandin)
- **Generic Available:** YES

Type 2 Oral Medications

- **Drug Class:** Thiazolidinedione (TZDs)
- **MOA:** A potent PPAR (gamma) agonist. Decreases insulin resistance in the periphery and decreases hepatic glucose output.
- **Generic (Brand) Name:** Pioglitazone (Actos)
- **Generic Available:** YES

Type 2 Oral Medications

- **Drug Class:** Alpha-Glucosidase inhibitors
- **MOA:** Lowers post-prandial blood glucose by competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolases; blocks the break down of simple and complex carbohydrate in the in the small intestine.
- **Generic (Brand) Name:** Acarbose (Precose); Miglitol (Glyset)
- **Generic Available:** YES

Type 2 Oral Medications

- **Drug Class:** Dipeptidyl peptidase-4 enzyme (DPP-4) inhibitors
- **MOA:** Prevents breakdown of GLP-1, a compound that lowers blood glucose
- **Generic (Brand) Name:** Alogliptin (Nesina); Linagliptin (Tradjenta); Saxagliptin (Onglyza); Sitagliptan (Januvia)
- **Generic Available:** NO

Type 2 Oral Medications

- **Drug Class:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors
- **MOA:** Blocks glucose from being reabsorbed by the kidneys (proximal renal tubules). Excess glucose is released in the urine.
- **Generic (Brand) Name:** Canagliflozin (Invokana); Dapagliflozin (Farxiga); Empagliflozin (Jardiance)
- **Generic Available:** NO

Two type 1 diabetics walk into a bar...

One asks the other, do you want to take a shot?

Type 2 Injected Medications

- **Drug Class:** GLP-1 receptor agonist
- **MOA:** Helps release insulin when blood glucose is high and lowers hepatic glucose production.
- **Generic (Brand) Name: Abiglutide (Eperzan, Tanzeum); Dulaglutide (Trulicity); Exenatide (Byetta); Exenatide ER (Bydureon); Liraglutide (Victoza); Lixisenatide (Adlyxin)**
- **Generic Available:** NO

Type 1 and 2 Injected Medication

- **Drug Class:** Amylinomimetic agent
- **MOA:** Amylin is responsible for the modulation of gastric emptying, prevention of the postprandial glucagon secretion, and satiety which leads to decreased caloric intake and potential weight loss
- **Generic (Brand) Name:** Pramlintide (Symlin)*
- **Generic Available:** NO

*Symlin is always used with insulin to help lower postprandial blood sugar.

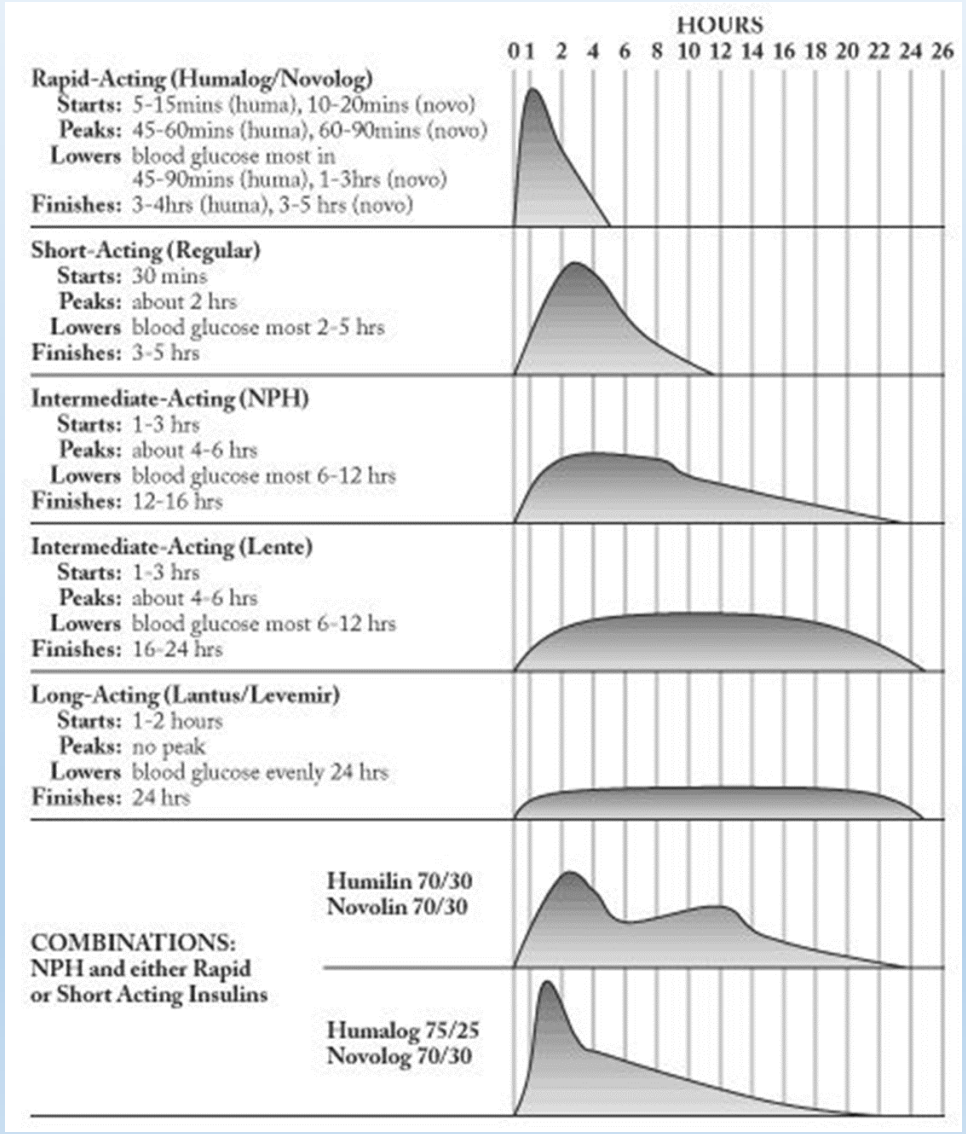
Insulin Considerations*

- Insulin pens eliminate many dosing challenges for patients.
- Clinicians need to understand how to use concentrated insulins effectively.
- Obesity-induced IR has led to high insulin requirements in a sizable percentage of people with T2DM
- Approximatly 35% of subjects with T2DM require basal insulin maintenance dose of 60 units.**
- Concentrated insulin uses:
  - Concentrated insulins enable higher dose of insulin in a single injection
  - Splitting doses can be cumbersome and painful

*http://www.medscape.org/viewarticle/864356

**Rodbard HW, et al. Endocr Pract. 2014;20:285-292

Insulin Therapy: Onset, Peak and Duration



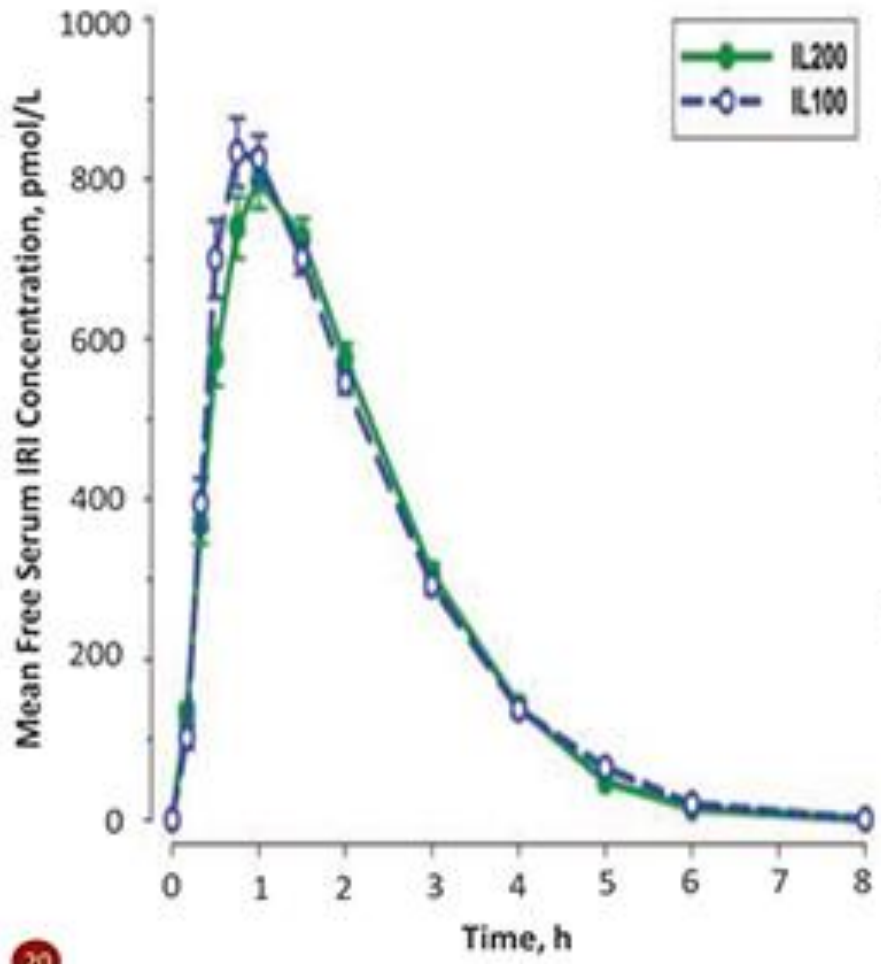
Rapid Acting Insulin

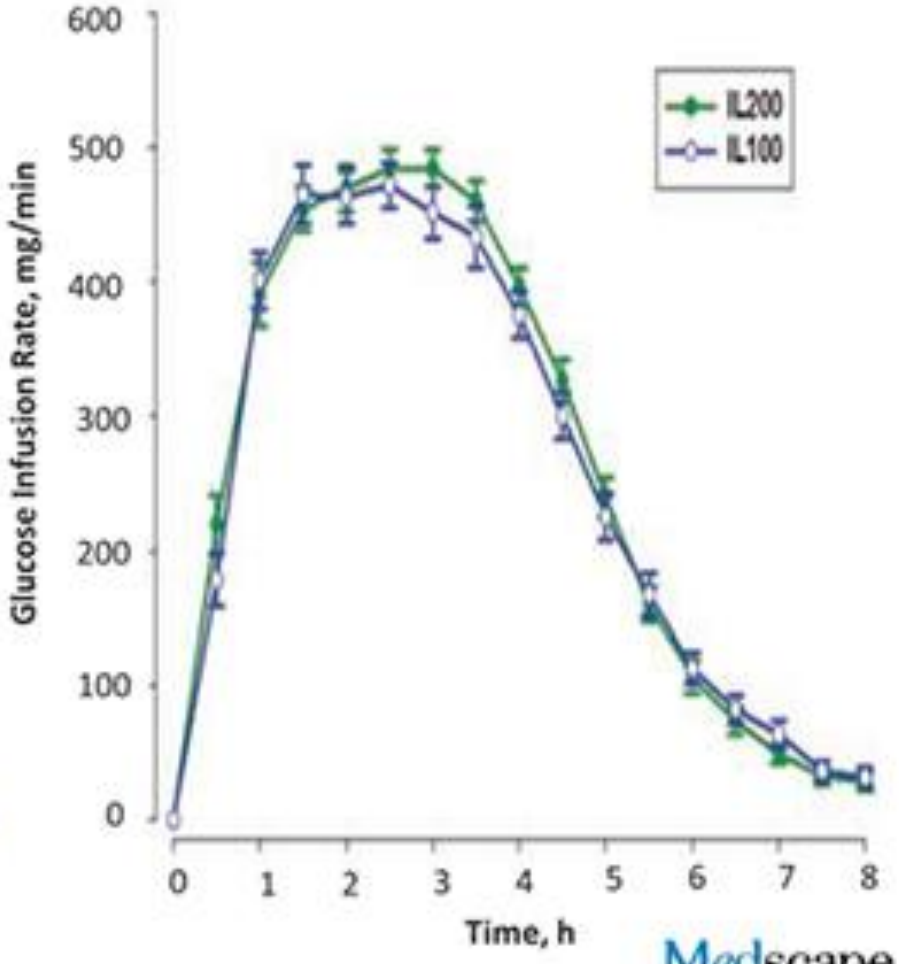
Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
Insulin aspart	NovoLog	NovoNordisk	Syringe; prefilled 300-unit disposable pen; reusable pen with 300-unit cartridges; pump	10 to 20 minutes	40 to 50 minutes	3 to 5 hours
Insulin glulisine	Apidra	Sanofi	Syringe; prefilled 300-unit disposable pen; pump	10 to 20 minutes	30 to 90 minutes	2 to 4 hours
Insulin human (inhaled powder)	Afrezza	MannKind Corp.	Inhaler with 4-, 8-, and 12-unit cartridges	3 to 7 minutes	12 to 15 minutes	2.5 to 3 hours
Insulin lispro (U-100 and U-200)	Humalog	Eli Lilly and Co.	Syringe; prefilled 3mL disposable pens: U100 (300-unit) [each box contains five pens] and U200 (600-unit) [each box contains two pens]; reusable pen with U100 (300-unit) 3mL cartridges; pump	10 to 20 minutes	30 to 90 minutes	3 to 5 hours

Humalog U-100 KwikPen

Humalog U-200 KwikPen

PK and PD Profiles of U100 and U200 Lispro





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de la Peña A, et al. *Clin Pharmacol Drug Dev*. 2016;5:69-75.

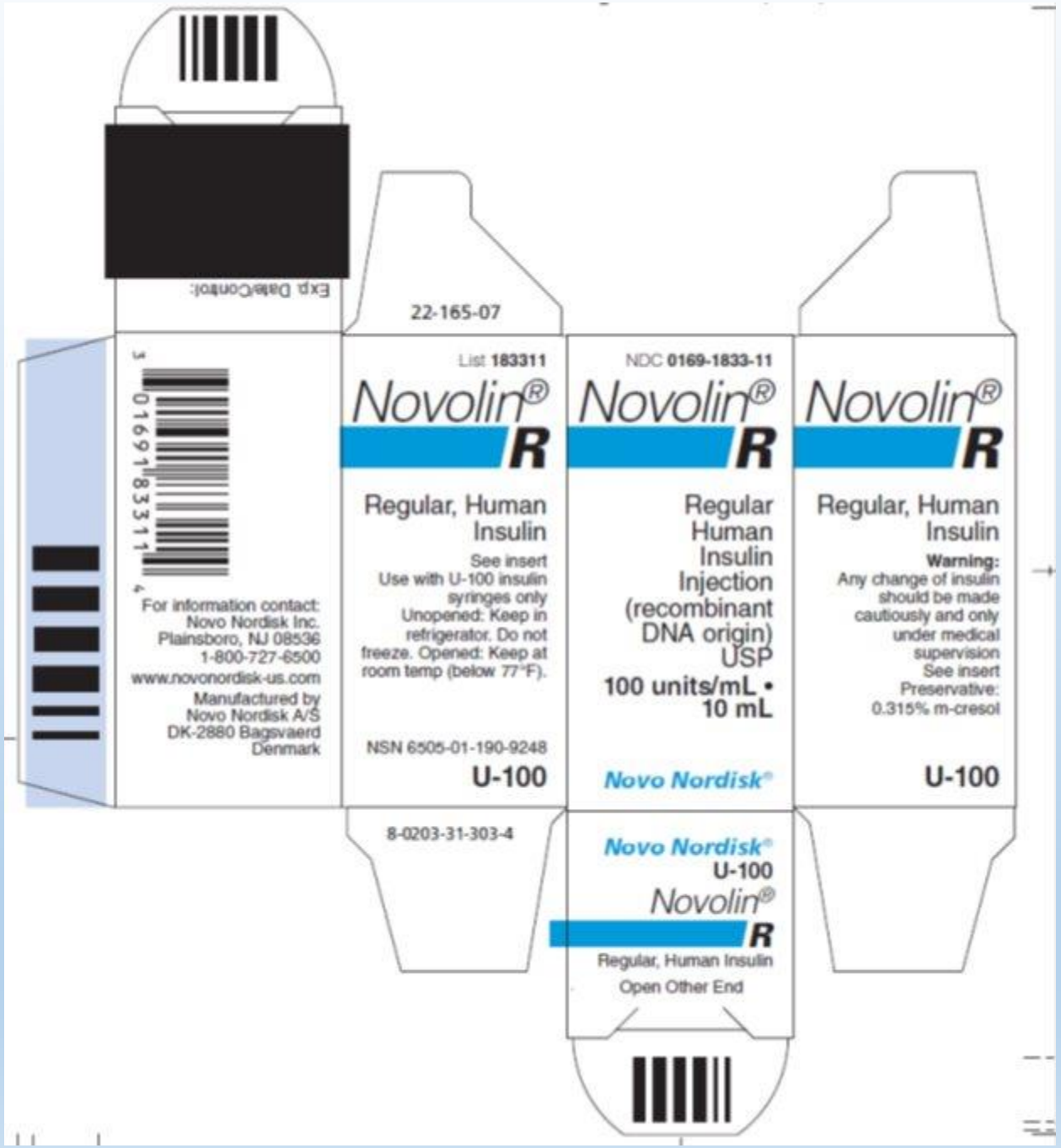
Medscape EDUCATION

Short-Acting Insulin

Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
Regular	Humulin R	Eli Lilly and Co.	Syringe	30 to 60 minutes	2 to 4 hours	5 to 8 hours
Regular (U-500)*	Humulin R U-500*	Eli Lilly and Co.	Concentrated U-500 injection solution 500U/ administer by Humulin R U-500 Syringe*; Concentrated U-500 KwikPen 500U/1mL	30 minutes	4 to 8 hours	Up to 24 hours
Regular	Novolin R, ReliOn Novolin R	NovoNordisk	Syringe	30 minutes	80 to 120 minutes	Up to 8 hours

*http://www.humulin.com/assets/pdf/DTC_2016_U500_Syringe_Patient_Starter_eBrochure.pdf
*http://www.consumermedsafety.org/insulin-safety-center/item/499

- The U-500 syringe has a green needle cap.
- The green collar carries an identifying U-500 Symbol.
- The U-500 syringe can dose up to 250 units of (0.5mL) U-500 insulin per injection.
- Each line on the U-500 syringe corresponds to 5 units of U-500 insulin.
- The safety and efficacy of HUMULIN R U-500 delivered by continuous subcutaneous infusion has not been determined.


Exp Date/Control:
22-165-07
List 183311
Novolin® R
Regular, Human Insulin
See insert
Use with U-100 insulin syringes only
Unopened: Keep in refrigerator. Do not freeze. Opened: Keep at room temp (below 77°F).
NSN 6505-01-190-9248
U-100
8-0203-31-303-4
3 01691833114
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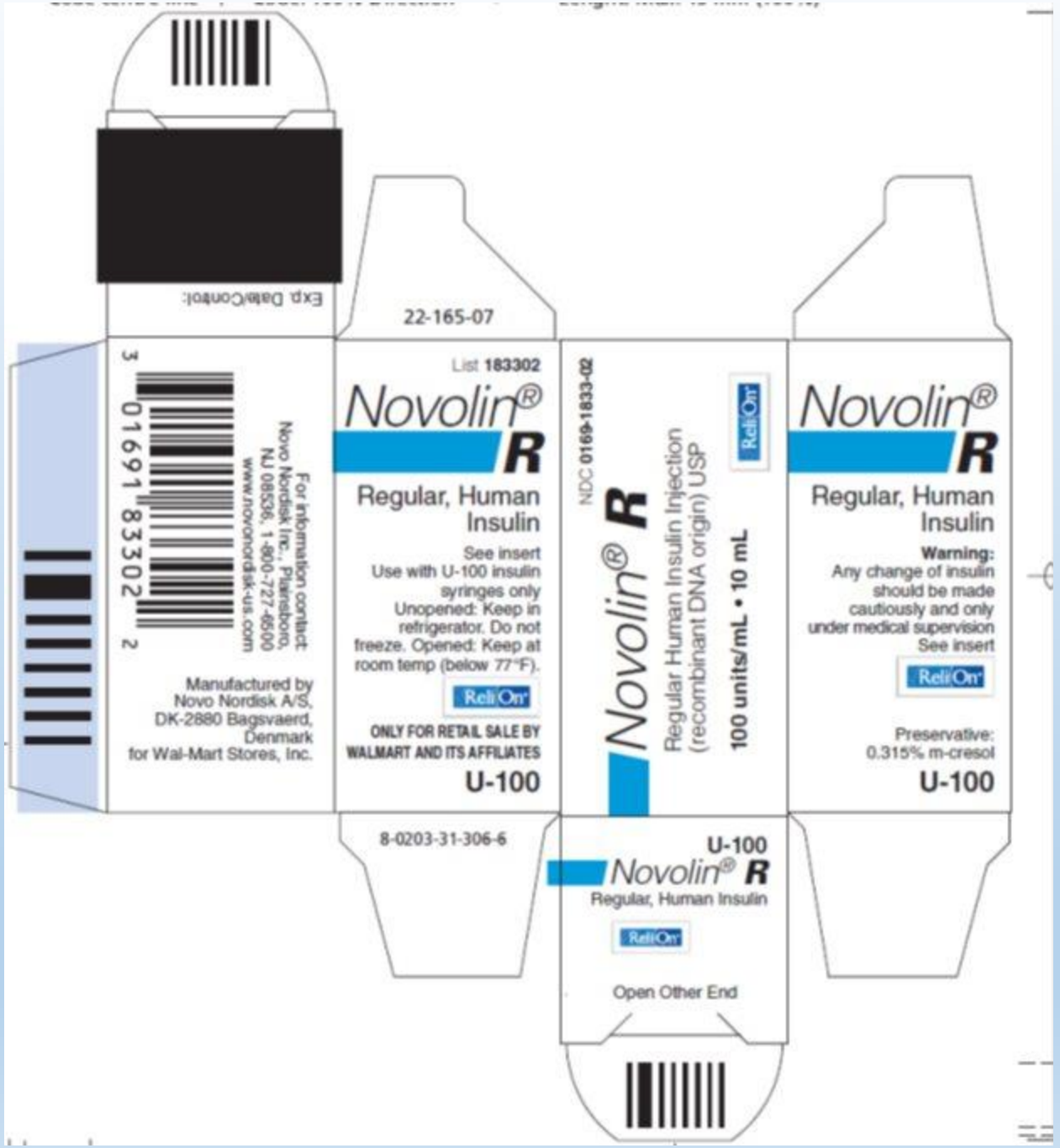
Novolin® R
Regular, Human Insulin
Open Other End
Novolin® R
Regular, Human Insulin
Warning:
Any change of insulin should be made cautiously and only under medical supervision
See insert
Preservative:
0.315% m-cresol
U-100


Exp. Date/Control:
3 01691 83302 2
For information contact:
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NJ 08536, 1-800-727-6500
www.novonordisk-us.com
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Denmark
for Wal-Mart Stores, Inc.
22-165-07
List 183302
Novolin® R
Regular, Human Insulin
See insert
Use with U-100 insulin syringes only
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ReliOn
ONLY FOR RETAIL SALE BY WALMART AND ITS AFFILIATES
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NDC 0169-1833-02
Novolin® R
Regular Human Insulin Injection
(recombinant DNA origin) USP
100 units/mL • 10 mL
ReliOn
U-100
Novolin® R
Regular, Human Insulin
ReliOn
Open Other End
Novolin® R
Regular, Human Insulin
Warning:
Any change of insulin should be made cautiously and only under medical supervision
See insert
ReliOn
Preservative:
0.315% m-cresol
U-100

Intermediate-Acting Insulin

Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
NPH	Humulin N	Eli Lilly and Co.	Syringe; prefilled 300-unit disposable pen	1 to 3 hours	8 hours	12 to 16 hours
NPH	Novolin N, ReliOn Novolin N	NovoNordisk	Syringe	90 minutes	4 to 12 hours	Up to 24 hours

Long-Acting Insulin

Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
Insulin detemir	Levemir	NovoNordisk	Syringe; prefilled 300-unit disposable pen	1.6 hours	No peak	Up to 24 hours
Insulin glargine	Lantus	Sanofi	Syringe; prefilled 300-unit disposable pen	1 hour	No peak	24 hours
Insulin glargine	Basaglar	Eli Lilly and Co.	Prefilled 300-unit disposable pen	1 hour	No peak	24 hours

CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 205692Orig1s000

Two minor differences between Basaglar and Lantus were noted. Basaglar contains ~~xxxxxxxxxxxxxxxxxxxxxxxxxx~~ process-related impurity not found to be present in Lantus. A slightly higher content of ~~xxxxxxxxxxx~~ ~~xxxxxxx~~ were observed in Basaglar compared to Lantus in accelerated stability studies. Dr. Ramaswamy states that this may not translate into significant difference during actual long-term storage condition. The Applicant suggests that the presence of ~~xxxxxxxxxxx~~ in the Lantus formulation ~~xxxxxxxxxxxxxxx~~. Basaglar does not contain ~~xxxxxxx~~ and the acceptance criteria set in the product specification for these impurities were found to be acceptable.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000SumR.pdf

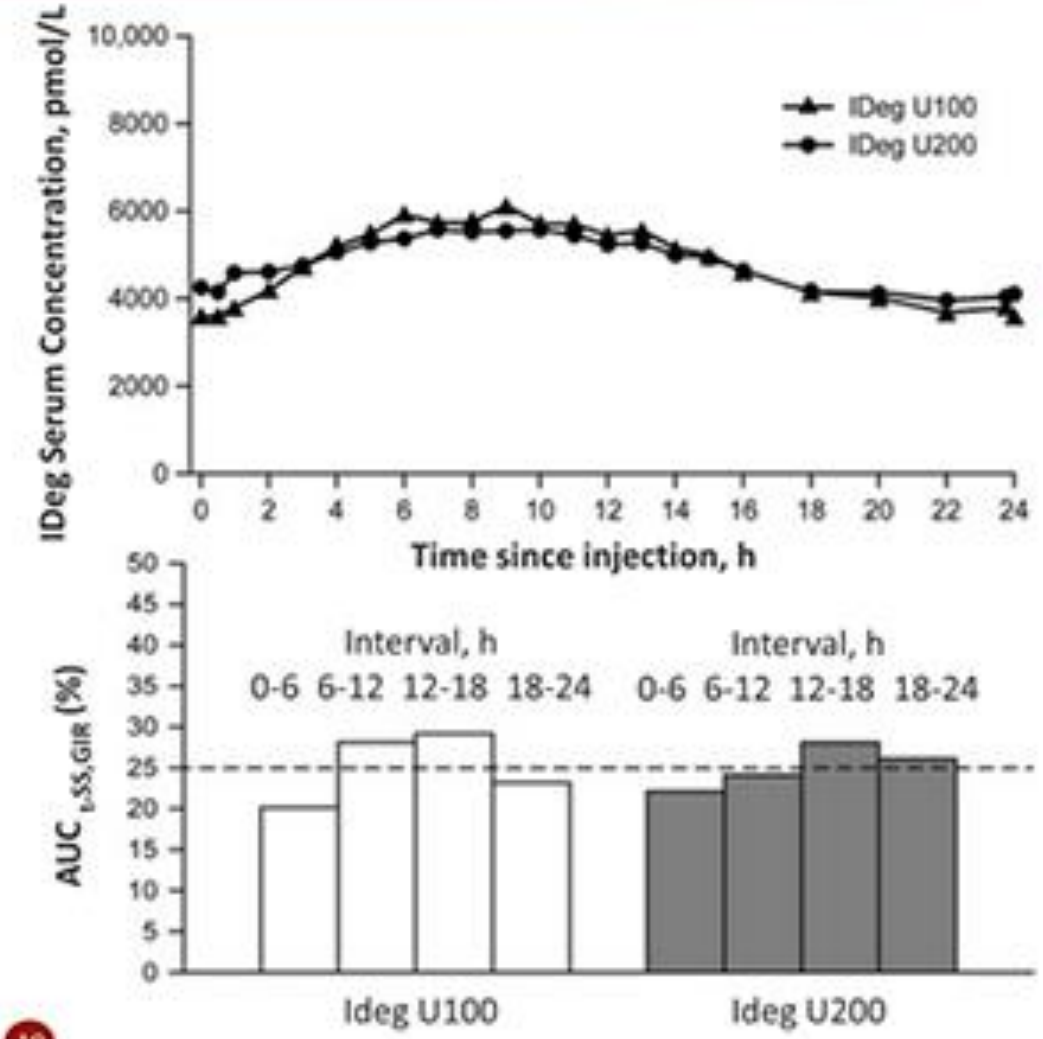
Ultra-Long-Acting Insulin

Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
Insulin degludec (U-100, U-200)	Tresiba	NovoNordisk	prefilled 100 units/mL (U-100) 3mL disposable pen [contains 300 units per pen], 1 box contains five prefilled pens; *prefilled 200 units/mL (U-200) 3mL disposable pen [contains 600 units per pen], 1 box contains 3 prefilled pens*	1 hour	No peak	At least 42 hours
Insulin glargine (U-300)	Toujeo	Sanofi	Prefilled 300 units/mL (U-300) 1.5mL [contains 450-units per pen] disposable pen, 1 box contains three or five prefilled pens.	6 hours	No peak	36 hours


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


Tresiba®
200
Tresiba®
100

PK/PD Profile of U200 Degludec Is Bioequivalent to U100 Degludec



- 8-day crossover euglycemic clamp study comparing PK profile of U100 to U200 IDeg at 0.4 U/kg in patients with T1D (n = 33) showed flat, stable PK/PD profiles for both insulin concentrations

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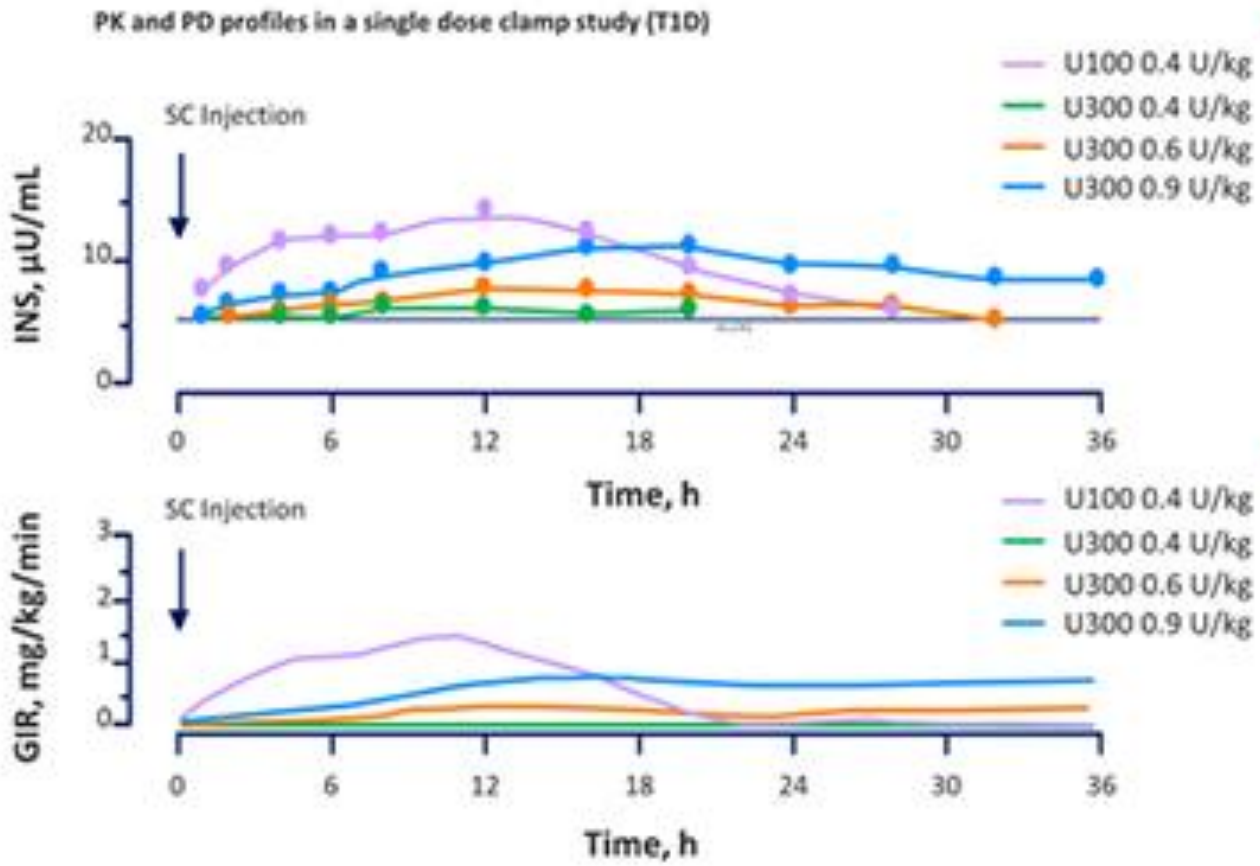
Korsatko S, et al. *Clin Drug Investig*. 2013;33:515-521.

Medscape EDUCATION

U300 Glargine: Single-Dose Clamp Profile



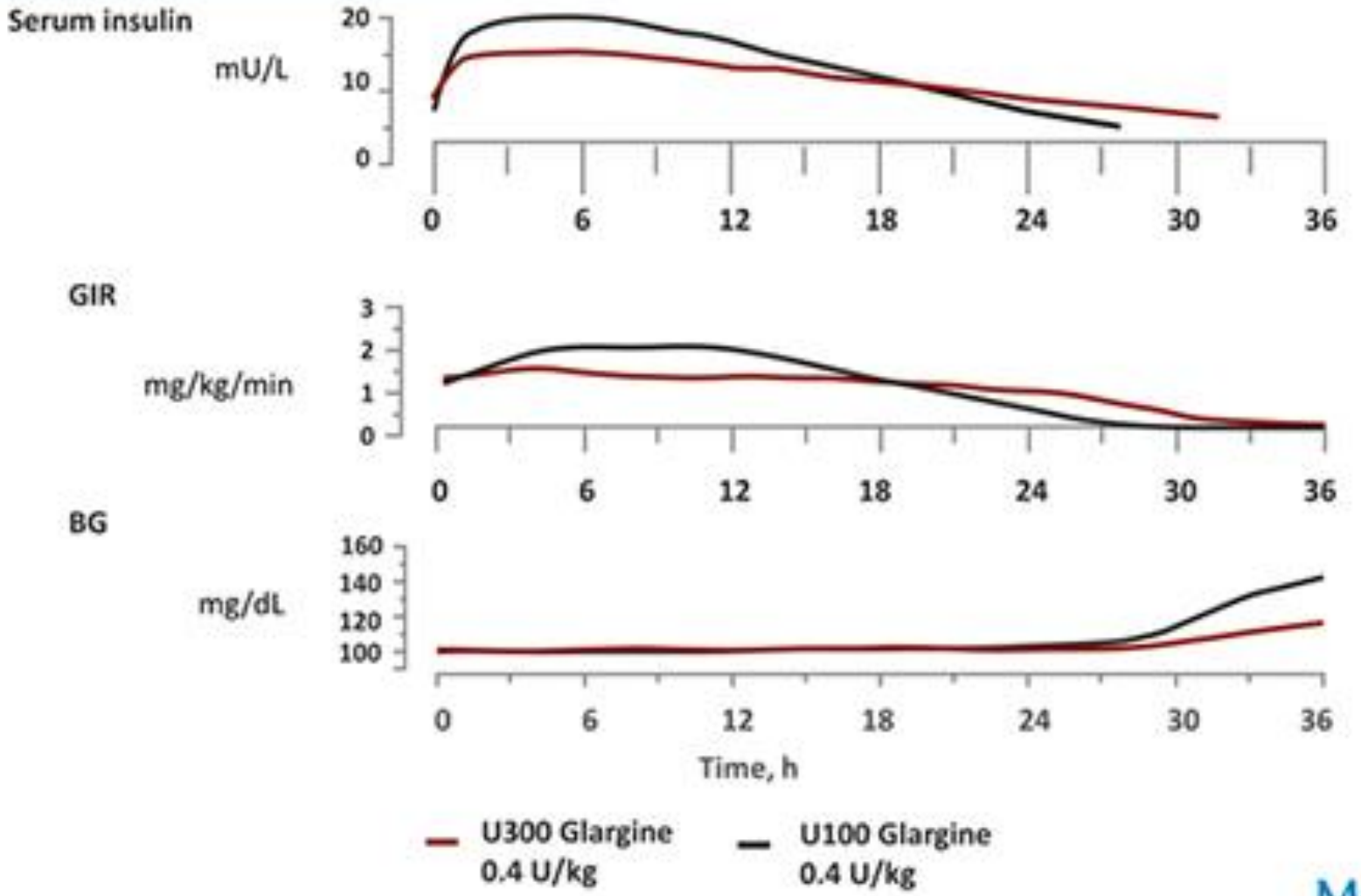
- U100 glargine and U300 glargine are not equivalent in bioavailability (exposure) and bio-efficacy (activity)
- Exposure and activity after administration of U300 were less by ~40% compared with exposure and activity after administration of the same amount (0.4 U/kg) from U100

16

Tillner J, et al. *Diabetes*. 2013;62:A234.

Medscape EDUCATION

U300 Glargine Has a Flatter, More Prolonged Time Action Profile Than U100 Glargine in Clamp Studies in T1D After 8 Days of Treatment



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Becker RH, et al. *Diabetes Care*. 2015;38:637-643.

Medscape EDUCATION

Insulin Mixtures

Generic Name	Brand Name	Manufacturer	Delivery	Onset	Peak	Duration
50% lispro protamine (NPL)/50%insulin lispro	Humalog Mix 50/50	Eli Lilly and Co.	Syringe; prefilled 300-unit disposable pen	10 to 15 minutes	1 to 4 hours	16 to 22 hours
75% lispro protamine (NPL)/25%insulin lispro	Humalog Mix 75/25	Eli Lilly and Co.	Syringe; prefilled 300-unit disposable pen	10 to 15 minutes	1 to 3 hours	16 to 22 hours
70% aspart protamine/30% insulin aspart	NovoLog Mix 70/30	NovoNordisk	Syringe; prefilled 300-unit disposable pen	10 to 20 minutes	1 to 3 hours	Up to 24 hours
70% NPH/ 30% Regular	Humulin 70/30	Eli Lilly and Co.	Syringe; prefilled 300-unit disposable pen	30 to 60 minutes	1 to 5 hours	12 to 16 hours
70% NPH/ 30% Regular	Novolin 70/30, ReliOn Novolin 70/30	NovoNordisk	Syringe	30 minutes	4.2 hours	Up to 24 hours

OH, YOU THINK THAT I AM NOT SPONTANEOUS ENOUGH?

HOW SELFISH OF ME TO CALCULATE, PLAN AND ACCOMMODATE FOR MY CHRONIC CONDITION EVERY SECOND OF EVERY DAY TO STAY ALIVE. WHAT AN INCONVENIENCE FOR YOU.

Pharmacologic Approaches to Glycemic Treatment

American Diabetes Association®

Evidence Grading System

A	• Clear evidence from well-conducted, generalizable RCTs, that are adequately powered, including • Evidence from a well-conducted multicenter trial or meta-analysis that incorporated quality ratings in the analysis; • Compelling nonexperimental evidence; • Supportive evidence from well-conducted RCTs that are adequately powered
B	• Supportive evidence from a well-conducted cohort studies • Supportive evidence from a well-conducted case-control study
C	• Supportive evidence from poorly controlled or uncontrolled studies • Conflicting evidence with the weight of evidence supporting the recommendation
E	• Expert consensus or clinical experience

Recommendations: Pharmacologic Therapy For Type 1 Diabetes (1)

- Most people with T1DM should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion (CSII). A
- Consider educating individuals with T1DM on matching prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. E
- Most individuals with T1DM should use insulin analogs to reduce hypoglycemia risk. A
- Individuals who have been successfully using CSII should have continued access after they turn 65 years old. E

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

That anger you feel..

when a pump or CGM alarm wakes you up in the middle of the night

DMT1 and 2
Pramlintide

- SYMLIN is an amylin analog indicated for patients with type 1 or type 2 diabetes who use mealtime insulin and have failed to achieve desired glycemic control despite optimal insulin therapy.(1)
- Delays gastric emptying, blunts pancreatic glucose secretion, enhances satiety
- Induces weight loss, lowers insulin dose
- Requires reduction in prandial insulin to reduce risk of severe hypos

(1)https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm404706.pdf

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

Recommendations: Pharmacologic Therapy For T2DM

- Metformin, if not contraindicated and
  if tolerated, is the preferred initial pharmacologic agent for T2DM. A
- Consider insulin therapy (with or without additional agents) in patients with newly dx'd T2DM who are markedly symptomatic and/or have elevated blood glucose levels (≥300 mg/dL) or A1C (≥10%). E

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

New Recommendation: Pharmacologic Therapy For T2DM

- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

New Recommendation: Pharmacologic Therapy For T2DM

- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

Recommendations: Pharmacological Therapy For T2DM

- If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or basal insulin. A
- Use a patient-centered approach to guide choice of pharmacologic agents. E
- Don’t delay insulin initiation in patients not achieving glycemic goals. B

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

Table 8.2—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S. (48)

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($5, $94)	2,000 mg
		850 mg (IR)	$108 ($5, $108)	2,550 mg
		1,000 mg (IR)	$86 ($4, $87)	2,000 mg
		500 mg (ER)	$90 ($82, $6,672)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	1,500 mg
		1,000 mg (ER)	$1,028 ($1,010, $7,213)	2,000 mg
Sulfonylureas (2nd Gen)	• Glyburide	5 mg	$94 ($64, $103)	20 mg
		6 mg (micronized)	$50 ($48, $71)	12 mg (micronized)
	• Glipizide	10 mg (IR)	$74 ($67, $97)	40 mg (IR)
		10 mg (XL)	$97	20 mg (XL)
	• Glimepiride	4 mg	$74 ($71, $198)	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$799 ($163, $878)	16 mg
	• Nateglinide	120 mg	$156	360 mg
TZDs	• Pioglitazone	45 mg	$349 ($348, $349)	45 mg
	• Rosiglitazone	4 mg	$355	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, 105)	300 mg
	• Miglitol	100 mg	$241	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$436	100 mg
	• Saxagliptin	5 mg	$436	5 mg
	• Linagliptin	5 mg	$428	5 mg
	• Alogliptin	25 mg	$436	25 mg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$679	3.75 g
		1.875 g suspension	$1,357	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$719	4.8 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$470	300 mg
	• Dapagliflozin	10 mg	$470	10 mg
	• Empagliflozin	25 mg	$470	25 mg
GLP-1 receptor agonists	• Exenatide	10 μg pen	$729	20 μg
	• Exenatide (extended-release)	2 mg powder for suspension or pen	$692	2 mg**
	• Liraglutide	18 mg/3 mL pen	$831	1.8 mg
	• Albiglutide	50 mg pen	$527	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$690	1.5 mg**
Amylin mimetics	• Pramlintide	120 μg pen	$2,124	120 μg/injection††

ER and XL, extended release; IR, immediate release; TZD, thiazolidinedione. †Calculated for 30 day supply (AWP unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP listed alone when only one product and/or price. *Utilized to calculate median AWP (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP calculated based on 120 μg three times daily.

Average wholesale price (AWP) does not necessarily reflect discounts, rebates, or other price adjustments that may affect the actual cost incurred by the patient but highlights the importance of cost considerations.

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

Insulin Therapy in T2DM

- The progressive nature of T2DM should be regularly & objectively explained to T2DM patients.
- Avoid using insulin as a threat, describing it as a failure or punishment.
- Give patients a self-titration algorithm.

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

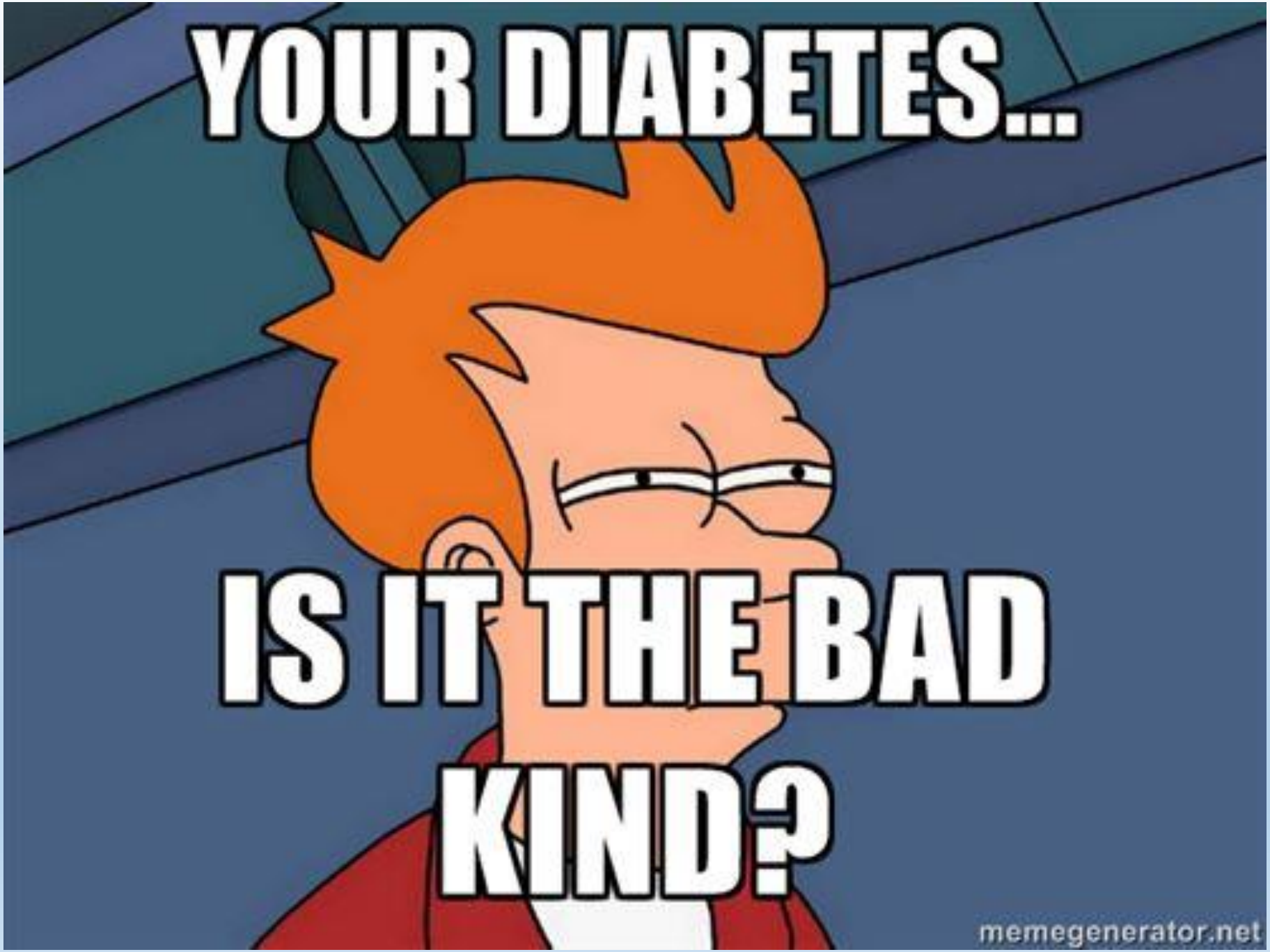
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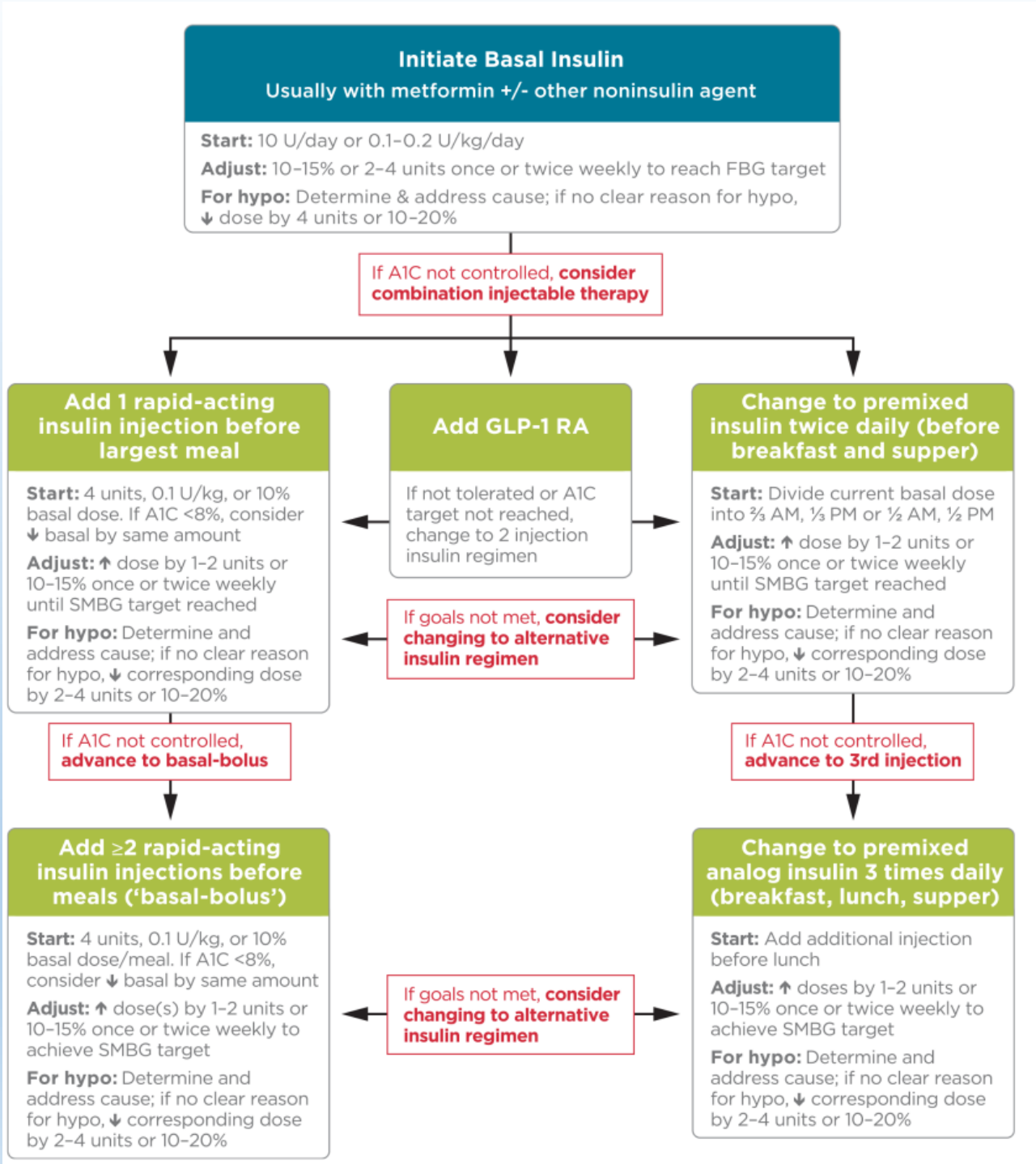
Table 8.3—Median cost of insulins in the U.S. calculated as average wholesale price per 1,000 units of specified dosage form/product (48)

Insulins	Compounds	Dosage form/product	Median AWP package price (min, max)*
Rapid-acting analogs			
	• Lispro	U-100 vial	$306
		U-100 3 mL cartridges	$306 ($306, $379)
		U-100 prefilled pen; U-200 prefilled pen	$394
	• Aspart	U-100 vial	$306
		U-100 3 mL cartridges	$380
		U-100 prefilled pen	$395
	• Glulisine	U-100 vial	$283
		U-100 prefilled pen	$365
	• Inhaled insulin	Inhalation cartridges	$557 ($453, $754)
Short-acting			
	• Human Regular	U-100 vial	$165
Intermediate-acting			
	• Human NPH	U-100 vial	$165
		U-100 prefilled pen	$350
Concentrated Human Regular insulin			
	• U-500 Human Regular insulin	U-500 vial	$165
		U-500 prefilled pen	$213
Basal analogs			
	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298
	• Detemir	U-100 vial; U-100 prefilled pen	$323
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355
Premixed products			
	• NPH/Regular 70/30	U-100 vial	$165
		U-100 prefilled pen	$350
	• Lispro 50/50	U-100 vial	$317
		U-100 prefilled pen	$394
	• Lispro 75/25	U-100 vial	$317
		U-100 prefilled pen	$394
	• Aspart 70/30	U-100 vial	$318
		U-100 prefilled pen	$395

AWP listed alone when only one product and/or price.

There have been substantial increases in the price of insulin in the past decade, and cost-effectiveness is an important consideration.

American Diabetes Association®


Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent
Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%
If A1C not controlled, consider combination injectable therapy
Add 1 rapid-acting insulin injection before largest meal
Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to basal-bolus
Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
Add GLP-1 RA
If not tolerated or A1C target not reached, change to 2 injection insulin regimen
If goals not met, consider changing to alternative insulin regimen
If goals not met, consider changing to alternative insulin regimen
Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to 3rd injection
Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Cardiovascular Disease and Risk Management

American Diabetes Association®

Cardiovascular Disease

- CVD is the leading cause of morbidity & mortality for those with diabetes.
- Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for ASCVD.
- Diabetes itself confers independent risk
- Control individual cardiovascular risk factors to prevent/slow CVD in people with diabetes.
- Systematically assess all patients with diabetes for cardiovascular risk factors.

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Hypertension

- Common DM comorbidity
- Prevalence depends on diabetes type, age, BMI, ethnicity
- Major risk factor for ASCVD & microvascular complications
- In T1DM, HTN often results from underlying kidney disease.
- In T2DM, HTN coexists with other cardiometabolic risk factors.

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Control

Systolic Targets:

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. A
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Control

Diastolic Targets:

- Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. A
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Control

Pregnant patients:

- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. E

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Treatment

- Patients with BP >120/80 should be advised on lifestyle changes to reduce BP. B
- Patients with confirmed BP >140/90 should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. A

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Treatment (2)

- Patients with confirmed office-based blood pressure >160/100mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. A
- Lifestyle intervention including:
  - Weight loss if overweight
  - DASH-style diet
  - Moderation of alcohol intake
  - Increased physical activity

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Treatment (3)

- Treatment for hypertension should include A
  - ACE inhibitor
  - Angiotensin II receptor blocker (ARB)
  - Thiazide-like diuretic
  - Dihydropyridine calcium channel blockers
- Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Treatment (4)

- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to– creatinine ratio ≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. B

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Hypertension/ Blood Pressure Treatment (5)

- If using ACE inhibitors, ARBs, or diuretics, monitor serum creatinine / eGFR & potassium levels. B

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Lipid Management

- In adults not taking statins, a screening lipid profile is reasonable (E):
  - At diabetes diagnosis
  - At the initial medical evaluation
  - And every 5 years, or more frequently if indicated
- Obtain a lipid profile at initiation of statin therapy, and periodically thereafter. E

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Lipid Management (2)

- To improve lipid profile in patients with diabetes, recommend lifestyle modification A, focusing on:
  - Weight loss (if indicated)
  - Reduction of saturated fat, trans fat, cholesterol intake
  - Increase of ω-3 fatty acids, viscous fiber, plant stanols/sterols
  - Increased physical activity

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Lipid Management (3)

- Intensify lifestyle therapy & optimize glycemic control for patients with: C
  - Triglyceride levels ≥150 mg/dL (1.7 mmol/L) and/or
  - HDL cholesterol <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women
- For patients with fasting triglyceride levels ≥ 500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce the risk of pancreatitis. C

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations for Statin Treatment in People with Diabetes

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Lipid Management (4)

- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). E
- Ezetimibe + moderate intensity statin therapy provides add'l CV benefit over moderate intensity statin therapy alone; consider for patients with a recent acute coronary syndrome w/ LDL ≥ 50mg/dL A or in patients with a history of ASCVD who can't tolerate high-intensity statin therapy. E

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Lipid Management (5)

- Combination therapy (statin/fibrate) doesn't improve ASCVD outcomes and is generally not recommended A. Consider therapy with statin and fenofibrate for men with *both* trigs ≥204 mg/dL (2.3 mmol/L) and HDL ≤34 mg/dL (0.9 mmol/L). B
- Combination therapy (statin/niacin) hasn't demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended. A
- Statin therapy is contraindicated in pregnancy. B

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

High- and Moderate-Intensity Statin Therapy*

High-Intensity Statin Therapy Lowers LDL by ≥50%	Moderate-Intensity Statin Therapy Lowers LDL by 30 - <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2-4 mg

* Once-daily dosing. XL, extended release

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Antiplatelet Agents

- Consider aspirin therapy (75–162 mg/day) C
- As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk
- Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Antiplatelet Agents (2)

- Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. C
  - Low risk: such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors)
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. A
- For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. B

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

10. Microvascular Complications and Foot Care

American Diabetes Association®

Neuropathy

Early recognition & management is important because:

1. DN is a diagnosis of exclusion.
2. Numerous treatment options exist.
3. Up to 50% of DPN may be asymptomatic.
4. Recognition & treatment may improve symptoms, reduce sequelae, and improve quality-of-life.

American Diabetes Association Standards of Medical Care in Diabetes.
Microvascular complications and foot care. Diabetes Care 2017; 40 (Suppl. 1): S88-S98

Recommendations: Neuropathy (2)

Treatment:

- Optimize glucose control to prevent or delay the development of neuropathy in patients with T1DM A & to slow progression in patients with T2DM. B
- Assess & treat patients to reduce pain related to DPN B and symptoms of autonomic neuropathy and to improve quality of life. E

American Diabetes Association Standards of Medical Care in Diabetes.
Microvascular complications and foot care. Diabetes Care 2017; 40 (Suppl. 1): S88-S98

New Recommendation: Neuropathy (3)

Treatment:

- Either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. A

American Diabetes Association Standards of Medical Care in Diabetes.
Microvascular complications and foot care. Diabetes Care 2017; 40 (Suppl. 1): S88-S98


THANK
YOU !

"Man, you guys should try this sometime.
You nerds are working waaaaay too hard."