Ultra-Rapid-Acting Insulins: How Fast Is Really Needed?

Eva Y. Wong[1] and Lisa Kroon[2]

OBJECTIVE. To review the new ultra-rapid-acting insulin analogs and describe the benefits and limitations compared with other bolus insulins.

SUMMARY. The options for bolus insulins, which are usually taken at mealtime or for correction of hyperglycemia, are expanding, with recent approvals of faster-acting insulin aspart and insulin lispro-aabc. These new-generation insulins contain additives that enhance absorption and accelerate onset of action. Clinical studies demonstrate that, although these insulins are faster acting, their efficacy for A1C lowering and safety in terms of hypoglycemia risk are similar to those of other available bolus insulin options such as rapid-acting insulin analogs. However, their use resulted in significant reductions in 1- and 2-hour postprandial glucose levels.

CONCLUSION. Novel ultra-rapid-acting insulins provide additional bolus insulin options, and their quick onset of action provides additional dosing flexibility for people with diabetes. Given their comparable efficacy and safety compared to other quick-acting insulins, health care providers should engage in shared decision-making with patients and their caregivers regarding possible use of ultra-rapid-acting insulin, taking into account their preferences, individualized considerations, and insurance formulary coverage. These new insulin formulations may be a suitable option for people with diabetes who are not able to achieve postprandial glycemic targets with other bolus insulins.

In the United States, there are 34.2 million children and adults (10.5% of the population) with diabetes. Approximately one in five people with diabetes have not been diagnosed (1). Because of autoimmune destruction of insulin-producing pancreatic β-cells, insulin is required for people with type 1 diabetes. Among those with type 2 diabetes, some patients may eventually need insulin therapy because of the progressive course of the disease and eventual β-cell failure (2). The prevalence of type 2 diabetes and diabetes-related complications is expected to increase continually based on increases in risk factors, including overweight and obesity, physical inactivity, and tobacco use, as well as common coexisting conditions such as hypertension and dyslipidemia (3).

In 1923, Iletin, a short-acting regular insulin derived from porcine pancreas, became the first type of insulin commercially available for diabetes management (4). Sixty years later, in 1983, recombinant human insulin produced by genetically altered bacteria was approved for the U.S. market (5). This recombinant formulation eliminated the risk of allergic reactions from earlier insulins derived from animal sources such as the bovine or porcine pancreas (5).

Further advancements in insulin therapy followed, with the approval of rapid-acting insulin analogs that better mimic the bolus secretion of physiological insulin (Figure 1). The first rapid-acting analog formulation, insulin lispro (Humalog), was approved in 1996, followed by insulin aspart (Novolog) in 2002, and insulin glulisine (Apidra) in 2004 (6). Most recently, a new class of insulins that have an even faster onset, referred to as "ultra-rapid-acting" insulins, have been introduced, with faster-acting insulin aspart (faster aspart; sold under the brand name Fiasp) approved in 2017 (7) and insulin lispro-aabc (URLi; sold under the brand name Lyumjev) approved in 2020 (8). With these new additions, clinicians have several bolus insulin options, with short-, rapid-, or ultra-rapid-acting time-action profiles, to assist patients with diabetes in managing postprandial glucose levels and making hyperglycemia corrections.

Ultra-Rapid-Acting Insulins

Faster Aspart

Insulin aspart is an analog of human insulin created by the replacement of amino acid proline (Pro) with aspartic acid (Asp) in the 28-amino-acid residues in the C-terminus of the β-chain (9). The substitution of ProB28 to

[1]Department of Pharmacy Practice, Marshall B. Ketchum University College of Pharmacy, Fullerton, CA; [2]Department of Clinical Pharmacy, University of California, San Francisco School of Pharmacy, San Francisco, CA

Corresponding author: Eva Y. Wong, ewong@ketchum.edu

https://doi.org/10.2337/cd20-0119

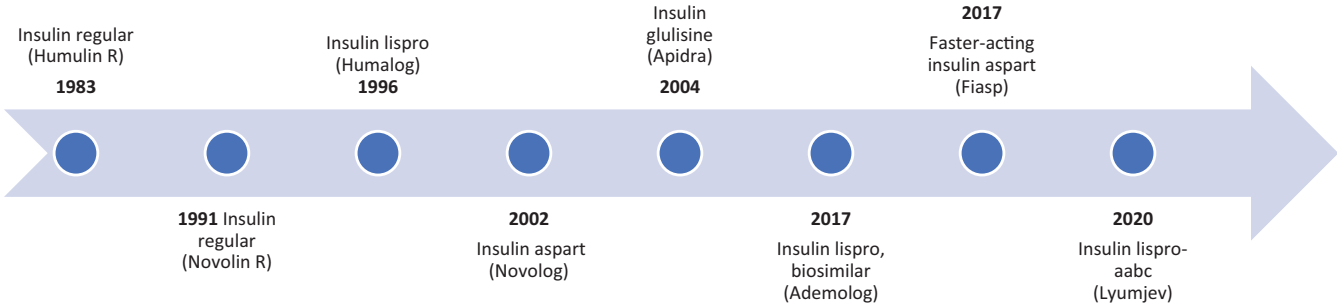

FIGURE 1 Timeline of U.S. Food and Drug Administration approval of bolus insulins (6).

AspB28 decreases the affinity of the insulin molecule to self-associate into hexamer formations. This change in the insulin structure results in a rapid onset of insulin activity compared with human insulin (10).

Faster aspart is similar to conventional insulin aspart (IAsp) except that it is formulated with niacinamide (vitamin B3) for faster absorption and a naturally occurring amino acid (L-arginine) to improve stability (11). These additives enable it to appear in the bloodstream in 2.5 minutes compared with 5.2 minutes with IAsp (12). Time to maximum insulin concentration is achieved 63 minutes after administration of faster aspart, which is 7.3 minutes earlier than with IAsp (12). Compared with that of IAsp, the pharmacodynamic profile of faster aspart includes a faster onset of action, occurring within 20–30 minutes, which is ∼5 minutes earlier; a faster time to peak effect, occurring in 1.5–2.2 hours, which is ∼10 minutes earlier; and a comparable duration of action (5 vs. 3–5 hours) (12). Faster aspart was initially approved in 2017 for the treatment of adults with diabetes, but in 2020, its indication was expanded to include children ≥2 years of age with diabetes (13).

In patients with type 1 diabetes, the results from the onset 1 clinical trial demonstrated that faster aspart was not inferior to IAsp in A1C reduction in the mealtime (administered 0–2 minutes before meals) and postmeal (administered 20 minutes after the start of meals) treatment groups (P <0.0001) (Table 1) (14). One- and two-hour postprandial glucose (PPG) increments were statistically significantly lower in favor of faster aspart given at mealtimes (P <0.0001 and P = 0.0089, respectively) (14). The initial study period was 26 weeks, which was extended an additional 26 weeks to determine whether faster aspart can maintain improved A1C glycemic control in the longer term. The full 52-week trial results were consistent with the initial 26-week findings in that patients treated with mealtime faster aspart achieved similar improvements in A1C in comparison with IAsp (P = 0.0424). Improvements were seen at the 1-hour PPG increment end point (−16.7 mg/dL [95% CI −28.5 to −5.0], P = 0.0054); however, there was no statistically significant difference in 2-hour PPG reduction (−7.2 mg/dL [95% CI −21.5 to 7.13], P = NS) (15). The results of the onset 1 trial favored faster aspart given at mealtime in comparison with postmeal timing, with varying degrees of 1- and 2-hour PPG A1C reduction, but similar long-term A1C reduction in patients with type 1 diabetes.

Faster aspart was tested in patients with type 2 diabetes in the onset 2 clinical trial, and results were similar to those in the onset 1 trial, demonstrating noninferiority for A1C reduction compared with IAsp (P <0.0001). Additionally, the improvement in 1-hour PPG increment was statistically significant (−10.63 mg/dL [95% CI −19.56 to −1.69], P = 0.0198); however, the 2-hour PPG increment did not reach statistical significance (−6.57 mg/dL [95% CI −14.54 to 1.41], P = 0.1063) (16). Overall, the results from the onset 1 and onset 2 clinical trials demonstrated noninferiority in A1C reduction, with greater 1- and 2-hour PPG reductions with faster aspart compared with IAsp; however, the 2-hour PPG reductions were not sustained in the extended 52-week onset 1 trial or the onset 2 trial. Accordingly, the results demonstrating glycemic efficacy similar to IAsp and potential for further lowering of PPG support the consideration of faster aspart as an alternative bolus insulin for patients with type 1 or type 2 diabetes.

URLi

Insulin lispro is an analog of human insulin created by two amino acid changes of proline (Pro) and lysine (Lys) in the 28- and 29-amino-acid residues in the C-terminus of the β-chain (9). There is an inversion of ProB28 to LysB28 and LysB29 to ProB29, which reduces the tendency for hexamer formations (9). As in other

TABLE 1 Summary of Ultra-Rapid-Acting Insulin Randomized Controlled Trials (14,15,16,20,21)

Trial	Patient Demographics	Intervention(s)	A1C Outcome (ETD, %)	PPG Outcome (ETD, mg/dL)
onset 1 (26 weeks)	• T1D; *n* = 1,143 • Duration of diabetes: 20.9 ± 12.9 vs. 19.5 ± 12.1 vs. 19.3 ± 11.8 years • Baseline A1C: 7.6 ± 0.7 vs. 7.6 ± 0.7 vs. 7.6 ± 0.7% • Baseline FPG: 151.4 ± 55.8 vs. 145.6 ± 57.6 vs. 141.8 ± 50.2 mg/dL	Faster aspart mealtime (0–2 minutes before meals) vs. faster aspart postmeal (20 minutes after meals) vs. IAsp mealtime (0–2 minutes before meals)	Faster aspart mealtime vs. IAsp: −0.15% (95% CI −0.23 to −0.07), *P* <0.0001, noninferiority confirmed Faster aspart postmeal vs. IAsp: 0.04% (95% CI −0.04 to 0.12), *P* <0.0001, noninferiority confirmed	1-hour PPG: Faster aspart mealtime vs IAsp: −25.44 (95% CI −36.12 to −14.76), *P* <0.0001 in favor of faster aspart mealtime Faster aspart postmeal vs. IAsp: 12.38 (95% CI 1.65–23.11), *P* = 0.0238 in favor of IAsp 2-hour PPG: Faster aspart mealtime vs. IAsp: −16.73 (95% CI −29.26 to −4.20), *P* = 0.0089 in favor of faster aspart mealtime 2-hour PPG: Faster aspart postmeal vs. IAsp: 1.08 (95% CI −11.49 to 13.66), *P* = NS
onset 1 (52 weeks; initial 26 weeks plus an additional 26 weeks)	• T1D; *n* = 761 • Duration of diabetes: 20.9 ± 12.9 vs. 19.8 ± 11.8 years • Baseline A1C: 7.6 ± 0.7 vs. 7.6 ± 0.7% • Baseline FPG: 151.4 ± 55.8 vs. 141.8 ± 50.2 mg/dL	Faster aspart mealtime (0–2 minutes before meals) vs. IAsp mealtime (0–2 minutes before meals)	Faster aspart mealtime vs. IAsp: −0.10% (95% CI −0.19 to −0.00), *P* = 0.0424, noninferiority confirmed	1-hour PPG: Faster aspart mealtime vs. IAsp: −16.7 (95% CI −28.5 to −5.0), *P* = 0.0054 in favor of faster aspart mealtime 2-hour PPG: Faster aspart mealtime vs. IAsp: −7.2 (95% CI −21.5 to 7.13), *P* = NS
onset 2 (26 weeks)	• T2D; *n* = 689 • Duration of diabetes: 13.2 ± 6.7 vs. 12.3 ± 6.3 years • Baseline A1C: 8.0 ± 0.7 vs. 7.9 ± 0.7% • Baseline FPG: 121.7 ± 32.7 vs. 122.7 ± 35.1 mg/dL	Faster aspart mealtime (0–2 minutes before meals) vs. IAsp mealtime (0–2 minutes before meals)	Faster aspart mealtime vs. IAsp: −0.02% (95% CI −0.15 to 0.10), *P* <0.0001, noninferiority confirmed	1-hour PPG: Faster aspart mealtime vs. IAsp: −10.63 (95% CI −19.56 to −1.69), *P* = 0.0198 in favor of faster aspart mealtime 2-hour PPG: Faster aspart mealtime vs. IAsp: −6.57 (95% CI −14.54 to 1.41), *P* = NS

Continued on p. 418»

»*Continued from p. 417*

TABLE 1 Summary of Ultra-Rapid-Acting Insulin Randomized Controlled Trials (14,15,16,20,21)

Trial	Patient Demographics	Intervention(s)	A1C Outcome (ETD, %)	PPG Outcome (ETD, mg/dL)
PRONTO-T1D (26 weeks)	• T1D; *n* = 1,222 • Duration of diabetes: 18.8 ± 12.3 vs. 18.8 ± 11.7 vs. 19.1 ± 12.0 years • Baseline A1C: 7.34 ± 0.65 vs. 7.36 ± 0.64 vs. 7.33 ± 0.67% • Baseline FPG: NR	URLi mealtime (0–2 minutes before meals) vs. URLi postmeal (20 minutes after meals) vs. lispro mealtime (0–2 minutes before meals)	URLi mealtime vs. lispro: −0.08% (95% CI −0.16 to 0.00), *P* = 0.06, noninferiority confirmed URLi postmeal vs. lispro: 0.13% (95% CI 0.04–0.22), *P* = 0.003, noninferiority confirmed	1-hour PPG: URLi mealtime vs. lispro: −27.9 (95% CI −35.3 to −20.5), *P* <0.001 in favor of URLi mealtime URLi postmeal vs. lispro: 13.1 (95% CI 5.0–21.4), *P* <0.05 in favor of lispro URLi postmeal vs. URLi mealtime: 41.0 (95% CI 32.9–39.1), *P* <0.001 in favor of URLi mealtime 2-hour PPG: URLi mealtime vs. lispro: −31.1 (95% CI −41.0 to −21.2), *P* <0.001 in favor of URLi mealtime URLi postmeal vs. lispro: 13.1 (95% CI −17.6 to 4.3), *P* = NS URLi postmeal vs. URLi mealtime: 24.5 (95% CI 13.5–35.5), *P* <0.001 in favor of URLi mealtime
PRONTO-T2D (26 weeks)	• T2D; *n* = 673 • Duration of diabetes: 16.4 ± 7.8 vs. 6.6 ± 7.9 years • Baseline A1C: 7.27 ± 0.68 vs. 7.31 ± 0.72% • Baseline FPG: NR	URLi mealtime (0–2 minutes before meals) vs. lispro mealtime (0–2 minutes before meals)	URLi mealtime vs. lispro: 0.06% (95% CI −0.05 to 0.16), *P* = NR, noninferiority confirmed	1-hour PPG: URLi mealtime vs. lispro: −11.9 (95% CI −18.2 to −5.4), *P* <0.001 in favor of URLi mealtime 2-hour PPG: URLi mealtime vs. lispro: −17.3 (95% CI −25.4 to −9.4), *P* <0.001 in favor of URLi mealtime

ETD, estimated treatment difference; FPG, fasting plasma glucose; NR, not reported; NS, not significant; T1D, type 1 diabetes; T2D, type 2 diabetes.

rapid-acting insulin analogs, this change in the insulin structure results in a faster onset of action (9).

URLi is an ultra-rapid-acting insulin formulated with treprostinil and citrate to improve the absorption of insulin lispro (17). Treprostinil is a prostacyclin analog that improves absorption via local vasodilation, and citrate allows for faster absorption via local vascular permeability (17). In a pharmacokinetic and pharmacodynamic study, URLi appears in the bloodstream ~1 minute after injection; its time to maximum concentration is 57 minutes after administration, which is 14 minutes faster in patients with type 1 diabetes and 11 minutes faster in patients with type 2 diabetes than convention insulin lispro (18). In comparison with insulin lispro, URLi's time to measurable effect is 20.1 minutes (vs. 31 minutes) in patients with type 1 diabetes and 32 minutes (vs. 45 minutes) in patients with type 2 diabetes. Its peak effect is 2–2.9 hours (vs. 2.4–2.8 hours), and its duration of action is 5 hours (vs. 5.5–6.6 hours) in patients with type 1 diabetes and 6.4 hours (vs. 6.7 hours) in patients with type 2 diabetes (19). At this time, URLi is approved only for adults with type 1 or type 2 diabetes.

The PRONTO-T1D and PRONTO-T2D clinical trials demonstrated that mealtime (administered 0–2 minutes before meals) and postmeal (administered 20 minutes after the start of meals) URLi levels were noninferior to conventional insulin lispro in the primary outcome of A1C for patients with type 1 or type 2 diabetes (20,21). In patients with type 1 diabetes, URLi achieved a similar end-of-treatment A1C change whether given at mealtime (−0.08% [95% CI −0.16 to 0.00], $P = 0.06$) or postmeal (0.13% [95% CI 0.04–0.22], $P = 0.003$). Improvements in 1-hour PPG (−27.9 mg/dL [95% CI −35.3 to −20.5], $P < 0.001$) and 2-hour PPG (−31.1 mg/dL [95% CI −41.0 to −21.2], $P < 0.001$) favored URLi given at mealtime (18). In patients with type 2 diabetes, URLi achieved similar end-of-treatment A1C change (0.06% [95% CI −0.05 to 0.16]), confirming noninferiority, and demonstrated statistical significance in reducing 1-hour PPG (−11.9 mg/dL [95% CI −18.2 to −5.4], $P < 0.001$) and 2-hour PPG (−17.3 mg/dL [95% CI −25.4 to −9.4], $P < 0.001$) excursions in patients with type 2 diabetes (21).

Place for Ultra-Rapid-Acting Insulins in Diabetes Treatment

The new generation of ultra-rapid-acting insulins, including faster aspart and URLi, offers additional bolus insulin options for patients with type 1 or type 2 diabetes. Advantages to these faster-acting agents include potential glycemic benefits in patients whose PPG is not at target, use in infusion pumps (only faster aspart is approved for such use at this time [22]), and their availability in convenient pen delivery devices.

These ultra-rapid-acting insulins provide a quick onset of action by achieving faster insulin absorption and faster times to maximum insulin concentration than other bolus insulins such as conventional short- and rapid-acting insulins. With faster aspart, the onset of action occurs 5 minutes earlier than with IAsp (23). URLi begins to act 10.9 minutes faster in patients with type 1 diabetes (24) and 13 minutes faster in patients with type 2 diabetes than conventional insulin lispro (19). With their faster onsets of action, these faster-acting bolus insulins provide patients the extra flexibility associated with injecting the medication just before or after meals. Their durations of action are similar to those of rapid-acting insulins, and, generally, there is no need to adjust basal insulin dosing when switching to the newer formulations. The onset 1 (26 weeks) and PRONTO-T1D trials demonstrated that faster aspart and URLi could be delivered either at mealtime (0–2 minutes before meals) or postmeal (20 minutes after meal), although mealtime administration provided statistically significant greater reductions in 1- and 2-hour PPG.

Compared with conventional rapid-acting analogs in phase 3, randomized, controlled trials, these newer faster-acting agents were confirmed to be noninferior in A1C reduction from baseline and achieved mixed results in reductions of 1- and 2-hour PPG (Table 1). Faster aspart demonstrated statistically significant greater reductions in both 1- and 2-hour PPG in the onset 1 (26 weeks) trial. Although there was a statistically significant reduction in 1-hour PPG compared with IAsp in the onset 1 (extended to 52 weeks) and onset 2 trials, the reductions in 2-hour PPG were not maintained and were not statistically significant in these trials. Alternatively, URLi demonstrated greater reductions in both 1- and 2-hour PPG in comparison with conventional lispro that were statistically significant in the PRONTO-T1D and PRONTO-T2D trials.

The results from these clinical studies suggest potential additional benefits in PPG control and may be useful in patients whose PPG targets have not been reached with other bolus insulin agents. These findings are especially relevant as more and more patients on insulin therapy self-monitor their glucose levels using continuous glucose monitoring (CGM) devices and tracking the metric of time in range.

These faster-acting agents are available in pen delivery devices, which are easier to use than traditional insulin vials and syringes. Both faster aspart and URLi are available in the standard U-100 (100 units/mL) concentration, but URLi also comes in a U-200 (200 units/mL) concentration for patients with higher bolus insulin dosage requirements. URLi U-100 is available in the Junior Kwikpen, which delivers 0.5-unit increments; the URLi U-100 KwikPen, URLi U-100 Tempo Pen, URLi U-200 Kwikpen, and faster aspart U-100 FlexTouch pen all deliver 1-unit increments (7,8).

Patients with diabetes who are using insulin infusion pumps may use either regular insulin or one of the rapid-acting insulin options. In clinical practice, ultra-rapid-acting insulins are also used in insulin pumps for the convenience and flexibility afforded by their quick action times. Based on the results of the onset 5 trial, the U.S. Food and Drug Administration approved faster aspart use in insulin pumps in October 2019 (22). With the recent approval of URLi, more studies are warranted to evaluate its efficacy and safety when used in insulin pumps.

Limitations and Additional Considerations

Additional considerations when evaluating the option of using a faster-acting insulin include the patient's age and pregnancy status, the ease of acquisition and cost of the medication, and the medication's long-term clinical and safety outcomes. Although faster aspart is approved for use in both children and adult patients (7), URLi is only approved for use in adult patients at this time; it has not yet been studied in children, and therefore its safety and efficacy in children with type 1 or type 2 diabetes are unknown (8).

Insulin therapy is the preferred treatment for managing hyperglycemia in women with gestational diabetes and in those with type 1 or type 2 diabetes during pregnancy, if pharmacotherapy is clinically indicated (25). The American College of Obstetricians and Gynecologists and The Endocrine Society recommend the use of insulin aspart and insulin lispro over regular insulin in patients with diabetes during pregnancy (26,27). However, these clinical guidelines were published before ultra-rapid-acting insulins became available. It is unknown whether faster aspart or URLi cross the placenta, and, because of methodological limitations, studies completed to date could not determine whether there are medication-related risks for major birth defects or miscarriage with these agents (7,8). Glycemic control in patients with diabetes is vital to maternal and fetal health and mitigates the risk for complications, including diabetic ketoacidosis, preterm delivery, preeclampsia, delivery complications, macrosomia, and major birth defects. Based on the limited data available, ultra-rapid-acting insulins cannot be recommended as a bolus option during pregnancy at this time, and rapid-acting insulins would be safer options.

Medication acquisition and costs should be considered when initiating or adjusting therapy. The costs of the ultra-rapid-acting insulin analogs are similar to those of rapid-acting insulin analogs (Table 2). For patients who have medication acquisition issues or for whom cost is a primary concern (e.g., those who self-pay for health care or are under-or uninsured), clinicians may consider prescribing more affordable bolus insulins such as regular human insulin, including the Walmart-branded ReliOn Novolin regular insulin (28) or the biosimilar insulin lispro analog Admelog (29). For patients with commercial or government insurance, the drug formulary should be reviewed first to select the plan's preferred bolus insulin agent.

With the steeply rising costs of insulins, many professional diabetes associations and patient advocacy groups, as well as the federal government, have pressured insulin manufacturers to reduce their insulin prices. Some manufacturers have reduced copayment programs (e.g., $35/month out of pocket), but not all people with diabetes are eligible (e.g., Medicare patients) (30). Fortunately, several Medicare Part D plans are now offering maximum copayments of $35 or less as of January 2021 (25).

Although ultra-rapid-acting insulins appear more quickly in the bloodstream and have a quicker time to first measurable effect, these characteristics have not been found to translate into clinically significant improvements in long-term glycemic control and safety outcomes. The clinical trials demonstrated that the efficacy of ultra-rapid-acting insulins in overall glycemic control as measured by A1C is comparable to that of their rapid-acting insulin counterparts. Secondary outcomes assessing medication safety found no significant treatment differences between the treatment groups in rates and incidences of severe, documented hypoglycemia. Ultimately, based on comparable efficacy and safety, all mealtime insulins may be considered viable options for bolus dosing in patients with type 1 or type 2 diabetes, depending on clinician judgment, glycemic response, and patient preference.

TABLE 2 Bolus Insulins Available in the United States (28,29,31,32)

Generic Name	Trade Name	Form	Concentration	Onset, minutes	Peak, minutes	Duration, hours	Cost (WAC) (29)
Ultra-rapid-acting insulins							
Faster aspart	Fiasp	Analog	U-100	16–20	63	5–7	$289.36/one 10-mL vial
							$558.83/five 3-mL FlexPens
							$537.47/five 3-mL Penfill cartridges
URLi	Lyumjev	Analog	U-100				$274.70/one 10-mL vial
							$530.40/five 3-mL KwikPens
			U-200	15–17	57	4.6–7.3	$424.32/two 3-mL KwikPens
Rapid-acting insulins							
Insulin aspart	Novolog	Analog	U-100	10–20	30–90	3–5	$289.36/one 10-mL vial
							$537.45/five 3-mL Penfill cartridges
							$558.83/five 3-mL FlexPens
Insulin glulisine	Apidra	Analog	U-100	10–20	30–90	3–5	$283.95/one 10-mL vial
							$548.52/five 3-mL SoloStar pens
Insulin lispro	Humalog	Analog	U-100	10–20	30–90	3–5	$137.35/one 10-mL vial
							$265.20/five 3-mL KwikPens or KwikPen Juniors
			U-200	15	30–90	3–5	$424.32/two 3-mL KwikPens
Insulin lispro, biosimilar	Admelog	Analog	U-100	15	30–90	3–5	$130.76/one 10-mL vial
							$39.23/one 3-mL vial
							$252.47/five 3-mL SoloStar pens
Insulin, inhaled	Afrezza	Human	U-100	12	35–55	1.5–4.5	$353.91/90 4-unit cartridges
							$707.82/90 8-unit cartridges
							$1,061.74/90 12-unit cartridges
Short-acting insulins							
Insulin, regular	Humulin R	Human	U-100	30–60	120–240	5–8	$148.70/one 10-mL vial
							$44.61/one 3-mL vial
	Novolin R	Human	U-100	30	80–120	Up to 8	$137.70/one 10-mL vial
							$25/one 10-mL vial (ReliOn) (29)

WAC, wholesale acquisition cost.

In collaboration with patients and caregivers, other important factors (e.g., patients' preferences, vision impairment, hearing impairment, and hand dexterity) should also be taken into consideration when starting or switching to a particular bolus insulin and delivery device.

Conclusion

The availability of ultra-fast-acting insulins provides additional bolus insulin alternatives for patients with type 1 or type 2 diabetes. Although this new generation, including faster aspart and URLi, allow for a quicker

rate of absorption and onset of action, the array of available bolus insulins all provide similar A1C-lowering effects and similar rates of severe, confirmed hypoglycemia in patients with diabetes. When initiating or switching to a new bolus insulin, health care providers can select from the bolus insulin options and should keep in mind patient-specific considerations and patients' insurance coverage. An ultra-rapid-acting insulin may be a good choice for patients with diabetes who are not reaching PPG targets with other bolus agents.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Both authors conceptualized, wrote, reviewed, and edited the manuscript. Both authors are guarantors of this work and, as such, had full access to all of the data reported and take responsibility for the integrity and accuracy of the article.

REFERENCES

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020*. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed 7 July 2020

2. American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S98–S110

3. Centers for Disease Control and Prevention, U.S. Diabetes Surveillance System. Diagnosed diabetes. Available from https://gis.cdc.gov/grasp/diabetes/diabetesatlas.html. Accessed 7 July 2020

4. White JR Jr. A brief history of the development of diabetes medications. Diabetes Spectr 2014;27:82–86

5. American Diabetes Association. Timeline. Available from https://www.diabetes.org/resources/timeline. Accessed 7 July 2020

6. U.S. Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Available from https://www.accessdata.fda.gov/scripts/cder/daf. Accessed 7 July 2020

7. Novo Nordisk. Fiasp [package insert]. Plainsboro, NJ, Novo Nordisk, 2019

8. Eli Lilly and Company. Lyumjev [package insert]. Indianapolis, IN, Eli Lilly and Company, 2020

9. Williams DA. *Foye's Principles of Medicinal Chemistry*. 7th ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2012

10. Mudaliar SR, Lindberg FA, Joyce M, et al. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care 1999;22:1501–1506

11. Kildegaard J, Buckley ST, Nielsen RH, et al. Elucidating the mechanism of absorption of fast-acting insulin aspart: the role of niacinamide. Pharm Res 2019;36:49

12. Heise T, Hövelmann U, Brøndsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. Diabetes Obes Metab 2015;17:682–688

13. Melillo G. FDA approves Fiasp for children with diabetes. Available from https://www.ajmc.com/newsroom/fda-approves-fiasp-for-children-with-diabetes. Accessed 8 July 2020

14. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950

15. Mathieu C, Bode BW, Franek E, et al. Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): a 52-week, randomized, treat-to-target, phase III trial. Diabetes Obes Metab 2018;20:1148–1155

16. Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. Diabetes Care 2017;40:951–957

17. Pratt E, Leohr J, Heilmann C, Johnson J, Landschulz W. Treprostinil causes local vasodilation, is well tolerated, and results in faster absorption of insulin lispro [Abstract]. Diabetes 2017;66(Suppl. 1):A253

18. Michael MD, Zhang C, Siesky AM, et al. Exploration of the mechanism of accelerated absorption for a novel insulin lispro formulation [Abstract]. Diabetes 2017;66(Suppl. 1):A250

19. Leohr J, Dellva MA, Coutant DE, et al. Pharmacokinetics and glucodynamics of ultra rapid lispro (URLi) versus Humalog (lispro) in patients with type 2 diabetes mellitus: a phase I randomised, crossover study. Clin Pharmacokinet 2020;59:1601–1610

20. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab 2020;22:1799–1807

21. Blevins T, Zhang Q, Frias JP, Jinnouchi H; PRONTO-T2D Investigators. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. Diabetes Care 2020;43:2991–2998

22. Klonoff DC, Evans ML, Lane W, et al. A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5). Diabetes Obes Metab 2019;21:961–967

23. Heise T, Linnebjerg H, Coutant D, et al. Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: a phase 1 randomized, crossover study. Diabetes Obes Metab 2020;22:1789–1798

24. Linnebjerg H, Zhang Q, LaBell E, et al. Pharmacokinetics and glucodynamics of ultra rapid lispro (URLi) versus Humalog (lispro) in younger adults and elderly patients with type 1 diabetes mellitus: a randomised controlled trial. Clin Pharmacokinet 2020;59:1589–1599

25. American Diabetes Association. 14. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S200–S210

26. American College of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131:e49–e64

27. Blumer I, Hadar E, Hadden DR, et al. Diabetes and pregnancy: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4227–4249

28. Fennell D. ReliOn insulin for $25 a vial at Walmart. Available from http://www.diabetesselfmanagement.com/blog/relion-insulin-for-25-a-vial-at-walmart. Accessed 6 October 2020

29. Micromedex. RED BOOK Online. Available from https://www.micromedexsolutions.com. Accessed 9 July 2020

30. Hayes TO, Farmer J. Insulin cost and pricing trends. Available from https://www.americanactionforum.org/research/insulin-cost-and-pricing-trends. Accessed 6 October 2020

31. American Diabetes Association. Consumer guide 2017: medications. Available from http://main.diabetes.org/dforg/pdfs/2017/2017-cg-medications.pdf. Accessed 20 June 2020

32. Sanofi. Admelog [package insert]. Bridgewater, NJ, Sanofi, 2019