Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Insulins

Date of Review: February 2020

Date of Last Review: September 2019
Literature Search: 05/01/19 – 12/31/19

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- Insulins were recently reviewed in September of 2019; therefore, minimal new evidence was available for review. Two randomized clinical trials, one new guideline (clinical context only), one systematic review and one new insulin formulation was identified.
- An intravenous formulation of insulin regular human, brand name Myxredlin®, was approved to be used in adults and children with diabetes mellitus for glucose control.
- No new evidence was identified that would result in changes to the preferred drug list (PDL).
- No additional research is needed.

Recommendations:
- No changes to the PDL are recommended based on the clinical review of efficacy and safety.
- After evaluation of costs in executive session , remove PA for insulin detemir pens (Levemir Flextouch®) and make forms of insulin lispro except Admelog® preferred.

Summary of Prior Reviews and Current Policy
- The last review in September 2019 found no clinically significant differences in glucose lowering between long-acting insulin products or between the short-acting insulin products.
- After executive session, insulin glulisine pens and vials, insulin regular U-500 pens, Humalog mix 75/25 and 50/50 KwikPens, and insulin detemir vials were designated as preferred products on the PDL.
- Newly approved products, Ademelog® and FIASP® were maintained as nonpreferred therapies.
- Non-preferred pens and cartridges require a prior authorization justifying the need for a non-preferred product.
- There is approximately 85% utilization of preferred insulin products; however, insulin costs are still substantial.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project,
Author: Kathy Sentena, PharmD

Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

CADTH – Clinical Review Report: Insulin degludec and liraglutide (Xultophy)

In 2019, CADTH reviewed the clinical effectiveness of combined insulin degludec (long-acting insulin product) and liraglutide (glucagon-like peptide 1 receptor agonists [GLP-1 RA]) for use in patients with type 2 diabetes mellitus (T2DM) to improve blood glucose levels.[1] Xultophy® has been previously reviewed and presented to the Pharmacy and Therapeutics Committee; therefore, only summary recommendations from CADTH will be provided. CADTH recommends insulin degludec/liraglutide, in combination with metformin (with or without a sulfonylurea) as an option for patients requiring basal insulin who have failed to meet target blood glucose goals on a GLP-1 RA, with or without other antidiabetic therapies. Benefit of therapy should be reassessed at 26 weeks.[1]

After review, three systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[2–4]

New Guidelines:

High Quality Guidelines: None identified

Additional Guidelines for Clinical Context:

American Diabetes Association – Standards of Medical Care in Diabetes -2020

The American Diabetes Association updates management standards for patients with diabetes mellitus on an annual basis.[5] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

New Formulations:

Insulin Regular human (Myxredlin®) – Myxredlin® is a short-acting insulin indicated for use to improve glycemic control in adults and pediatric patients with diabetes mellitus.[6] Myxredlin® is formulated in a sodium chloride injection for intravenous use only.

New Indications:

Insulin aspart (FIASP®) – Rapid-acting insulin aspart was approved for use in pediatric patients based on a 26-week, randomized controlled trial in 777 patients with type 1 diabetes mellitus (T1DM).[7] Rapid acting insulin aspart was compared to insulin aspart (Novolog®), in a blinded manner at mealtimes. The third arm was an open-label rapid acting insulin aspart given post-meal. All regimens were given with insulin degludec once daily. The primary outcome was HbA1c lowering. Both doses of rapid-acting insulin aspart were shown to be noninferior to insulin aspart.[7]

New FDA Safety Alerts: None identified.

References:

1. Canadian Agency for Drugs and Technologies in Health. Clinical review report: Xultophy. CADTH Common Drug Review. December 2019. Available at: https://www.cadth.ca/sites/default/files/cdr/clinical/sr0599-xultophy-clinical-review-report.pdf. Accessed 31 December, 2019.

2. Maiorino M, Chiodini P, Bellastella G, et al. The good comparisons: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. A systematic review and meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice. 2019;154:101-115.

3. Santos L, Leite J, Barbosa L, et al. Effectiveness of insulin analogs compared with human insulins in pregnant women with diabetes mellitus: systematic review and meta-analysis. Rev Bras Gineco Obstet. 2019;41:104-115.

4. Canadian Agency for Drugs and Technologies in Health. Long-acting insulin analogues versus human NPH insulin for adults with type 2 diabetes and unresponsiveness to non-insulin therapies: clinical effectiveness, cost-effectiveness, and guidelines. CADTH Rapid Response Report. 3 May 2019. Available at:https://www.cadth.ca/sites/default/files/pdf/htis/2019/RB1331%20LA%20Insulin%20versus%20NPH%20Final.pdf. Accessed 31 December 2019.

5. American Diabetes Association. Pharmacological approaches to glycemic treatment: standards of medical care in diabetes - 2020. Diabetes Care. 2020;43:S98-S110.

6. Myxredlin (insulin human in sodium chloride injection) [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation. June 2019.

7. Fiasp (insulin aspart) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk, December 2019.

8. Dovc K, Piona C, Mutlu G, et al. Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapies in type 1 diabetes: a double-blind randomized crossover trial. Diabetes Care. 2019. published ahead of print. doi:10.2337/dc19-0895/-/DC1.

9. Bode B, Iotova V, Kovarenko M, et al. Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both in combination with insulin degludec, in children and adolescents with type 1 diabetes: the onset 7 trial. Diabetes Care. 2019;42:1255-1262.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
insulin aspart	NOVOLOG	CARTRIDGE	SQ	Y
insulin aspart	NOVOLOG FLEXPEN	INSULN PEN	SQ	Y
insulin aspart	NOVOLOG	VIAL	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	VIAL	SQ	Y
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	SQ	Y
insulin detemir	LEVEMIR	VIAL	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	SQ	Y
insulin glulisine	APIDRA SOLOSTAR	INSULN PEN	SQ	Y
insulin glulisine	APIDRA	VIAL	SQ	Y
insulin lispro	HUMALOG	VIAL	SQ	Y
insulin lispro	INSULIN LISPRO	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	VIAL	SQ	Y
insulin NPH human isophane	HUMULIN N	VIAL	SQ	Y
insulin NPH human isophane	NOVOLIN N	VIAL	SQ	Y
insulin regular, human	HUMULIN R U-500 KWIKPEN	INSULN PEN	SQ	Y
insulin regular, human	HUMULIN R	VIAL	IJ	Y
insulin regular, human	NOVOLIN R	VIAL	IJ	Y
insulin regular, human	HUMULIN R U-500	VIAL	SQ	Y
insulin aspart (niacinamide)	FIASP PENFILL	CARTRIDGE	SQ	N
insulin aspart (niacinamide)	FIASP FLEXTOUCH	INSULN PEN	SQ	N
insulin aspart (niacinamide)	FIASP	VIAL	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	SQ	N
insulin degludec	TRESIBA	VIAL	SQ	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	SQ	N

insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	SQ	N
insulin lispro	HUMALOG	CARTRIDGE	SQ	N
insulin lispro	HUMALOG JUNIOR KWIKPEN	INS PEN HF	SQ	N
insulin lispro	ADMELOG SOLOSTAR	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-200	INSULN PEN	SQ	N
insulin lispro	INSULIN LISPRO KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	ADMELOG	VIAL	SQ	N
insulin NPH human isophane	HUMULIN N KWIKPEN	INSULN PEN	SQ	N
insulin regular, human	AFREZZA	CART INHAL	IH	N
insulin regular in 0.9 % NaCl	MYXREDLIN	PLAST. BAG	IV	

Appendix 2: New Comparative Clinical Trials

A total of fifty citations were manually reviewed from the initial literature search. After further review, forty-eight citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Dovc, et al[8] DB, RCT, CO	Faster insulin aspart vs. Insulin aspart (both administered via a fully closed-loop insulin therapy)	Adult patients with T1DM on an insulin pump (n=20)	Difference in blood glucose levels based time in range (70-180 mg/dL) over 27 hours based on glucose sensor data	Time in range: Faster insulin aspart: 53.3% Insulin aspart: 57.9% P=0.170 *No significant difference between treatments.*
Bode, et al[9] MC, RCT, DB	Mealtime fast-acting insulin aspart* vs. Mealtime insulin aspart* or Post-meal open-label faster insulin aspart* * All with insulin degludec 26-week (with 12-week run in)	Children and adolescents (1 to <18 years) with T1DM (n=777)	Change in baseline HbA1c after 26 weeks	Mealtime fast acting insulin aspart: -0.2% Mealtime insulin aspart: 0.0% Post-meal fast acting insulin aspart: 0.1% <u>Mealtime fast acting aspart vs. mealtime insulin aspart</u> TD -0.17% (95% CI, -0.30 to -0.03) P < 0.001 for non-inferiority, p=0.007 for superiority <u>Open-label post-meal insulin aspart vs. mealtime insulin aspart</u> TD 0.13% (95% CI, -0.01 to 0.26) P < 0.001 for non-inferiority *Fast-acting insulin aspart was noninferior to insulin aspart. Mealtime fast-acting insulin aspart was also superior to mealtime insulin aspart.*

Abbreviations: CI = confidence interval; CO = crossover; DB = double-blind; MC = multi-center; RCT = randomized clinical trial; T1DM = type 1 diabetes mellitus; TD = treatment difference

Appendix 3: Abstracts of Comparative Clinical Trials

Faster Compared With Standard Insulin Aspart During Day-and-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial
Klemen Dovc , Claudia Piona , Gül Yeşiltepe Mutlu , Natasa Bratina , Barbara Jenko Bizjan , Dusanka Lepej , Revital Nimri , Eran Atlas , Ido Muller , Olga Kordonouri , Torben Biester , Thomas Danne , Moshe Phillip , Tadej Battelino

Objective: We evaluated the safety and efficacy of day-and-night fully closed-loop insulin therapy using faster (Faster-CL) compared with standard insulin aspart (Standard-CL) in young adults with type 1 diabetes.
Research design and methods: In a double-blind, randomized, crossover trial, 20 participants with type 1 diabetes on insulin pump therapy (11 females, aged 21.3 ± 2.3 years, HbA_{1c} 7.5 ± 0.5% [58.5 ± 5.5 mmol/mol]) underwent two 27-h inpatient periods with unannounced afternoon moderate-vigorous exercise and unannounced/uncovered meals. We compared Faster-CL and Standard-CL in random order. During both interventions, the fuzzy-logic control algorithm DreaMed GlucoSitter was used. Glucose sensor data were analyzed by intention-to-treat principle with the difference (between Faster-CL and Standard-CL) in proportion of time in range 70-180 mg/dL (TIR) over 27 h as the primary end point.
Results: The proportion of TIR was similar for both arms: 53.3% (83% overnight) in Faster-CL and 57.9% (88% overnight) in Standard-CL ($P = 0.170$). The proportion of time in hypoglycemia <70 mg/dL was 0.0% for both groups. Baseline-adjusted interstitial prandial glucose increments 1 h after meals were greater in Faster-CL compared with Standard-CL ($P = 0.017$). The gaps between measured plasma insulin and estimated insulin-on-board levels at the beginning, at the end, and 2 h after the exercise were smaller in the Standard-CL group ($P = 0.029$, $P = 0.003$, and $P = 0.004$, respectively). No severe adverse events occurred.
Conclusions: Fully closed-loop insulin delivery using either faster or standard insulin aspart was safe and efficient in achieving near-normal glucose concentrations outside postprandial periods. The closed-loop algorithm was better adjusted to the standard insulin aspart.

Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec, in Children and Adolescents With Type 1 Diabetes: The Onset 7 Trial
Bruce W Bode , Violeta Iotova , Margarita Kovarenko , Lori M Laffel , Paturi V Rao , Srikanth Deenadayalan , Magnus Ekelund , Steffen Falgreen Larsen , Thomas Danne

Objective: To confirm efficacy and safety of fast-acting insulin aspart (faster aspart) versus insulin aspart (IAsp), both with basal insulin degludec, in a pediatric population with type 1 diabetes.
Research design and methods: After a 12-week run-in, this treat-to-target, 26-week, multicenter trial randomized participants (1 to <18 years) to double-blind mealtime faster aspart ($n = 260$), mealtime IAsp ($n = 258$), or open-label postmeal faster aspart ($n = 259$). The primary end point was change from baseline in glycated hemoglobin (HbA_{1c}) after 26 weeks of treatment. All available information regardless of treatment discontinuation was used for the evaluation of treatment effect.
Results: At week 26, mealtime and postmeal faster aspart were noninferior to IAsp regarding change from baseline in HbA_{1c} ($P < 0.001$ for noninferiority [0.4% margin]), with a statistically significant difference in favor of mealtime faster aspart (estimated treatment difference -0.17% [95% CI -0.30; -0.03], -1.82 mmol/mol [-3.28; -0.36]; $P = 0.014$). Change from baseline in 1-h postprandial glucose increment significantly favored mealtime faster aspart versus IAsp at breakfast, main evening meal, and over all meals ($P < 0.01$ for all). No statistically significant differences in the overall rate of severe or blood glucose-confirmed hypoglycemia were observed. Mean total daily insulin dose was 0.92 units/kg for mealtime faster aspart, 0.92 units/kg for postmeal faster aspart, and 0.88 units/kg for mealtime IAsp.
Conclusions: In children and adolescents with type 1 diabetes, mealtime and postmeal faster aspart with insulin degludec provided effective glycemic control with no additional safety risks versus IAsp. Mealtime faster aspart provided superior HbA_{1c} control compared with IAsp.

Appendix 4: Medline Search Strategy
Database(s): Ovid MEDLINE(R) ALL 1946 to December 31, 2019
Search Strategy:

#	Searches	Results
1	insulin aspart.mp. or Insulin Aspart/	1118
2	Insulin Detemir/ or insulin detemir.mp.	820
3	insulin glargine.mp. or Insulin Glargine/	2585
4	Insulin Lispro/ or insulin lispro.mp.	1131
5	insulin NPH.mp. or Insulin, Isophane/	1092
6	insulin regular.mp. or Insulin/	185244
7	insulin degludec.mp.	541
8	1 or 2 or 3 or 4 or 5 or 6 or 7	187543
9	limit 8 to (english language and humans and yr="2019 -Current")	1045
10	limit 9 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	50

Appendix 5: Key Inclusion Criteria

Population	Patients with T1DM and T2DM
Intervention	Insulins
Comparator	Active treatment comparisons or placebo
Outcomes	Mortality, micro- and macrovascular complications, glucose lowering, hypoglycemia
Timing	New onset or established diabetes
Setting	Outpatient

Insulins

Goal:
Provide evidence-based and cost-effective insulin options to patients with diabetes mellitus.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred insulin vials
- Non-preferred short-acting insulin pens
- All pre-filled insulin pens, cartridges and syringes with the exception of insulin lispro protamine-lispro (Humalog® Mix 75-25 Kwikpen), insulin lispro protamine-lispro (Humalog® Mix 50-50 Kwikpen), insulin detemir (Levemir® Flextouch), insulin glargine (Lantus SoloSTAR®)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Go to #4
4. Is the request for an insulin pen or cartridge?	**Yes:** Go to #5	**No:** Approve for up to 12 months

Approval Criteria		
5. Has the patient tried and failed or have contraindications to any of the preferred pens or cartridges listed above?	**Yes:** Go to #6	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products
6. Will the insulin be administered by the patient or a non-professional caregiver **AND** do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is a child less than 18 years of age?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

P&T / DUR Review: 2/20(KS); 9/19; 11/18; 9/17; 3/16; 11/15; 9/10
Implementation: 11/1/2019; 11/1/17; 10/13/16; 1/1/11