

Insulin Lispro 200units/mL (Humalog) KwikPen Abbreviated Review

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

FDA Approval Information

Indication(s) Under Review	Rapid-acting human insulin analog to improve glycemic control in adults and children with type 2 diabetes.
Dosage Form(s) Under Review	200 units/mL insulin lispro in 3mL KwikPen disposable prefilled pen
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS
Pregnancy Rating	Category B

Executive Summary	
Efficacy	There are no clinical trials. The only trial is a pharmacokinetic/pharmacodynamics euglycemic clamp study. Lispro U-200 and lispro U-100 were found to be bioequivalent after a 20U subcutaneous injection in healthy subjects.
Safety	Concern for dosing errors Confusion with Lispro-100 (although label colors are different for the 2 products)
Other Considerations	<ul style="list-style-type: none"> • Has not been studied in patients with insulin resistance (e.g., total daily insulin dose >200U/d) • CANNOT be administered via continuous subcutaneous infusion pump • CANNOT be administered intravenously • Do NOT mix with any other insulin • Not intended as a replacement for those requiring U500 insulin • Is administered via disposable prefilled KwikPen • Up to 60 units can be administered in a single injection • High cost

Background

Purpose for Review	The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating insulin lispro U-200 for possible addition to the VA National Formulary	
Other Therapeutic Options	Formulary Alternatives	Other Considerations
	Insulin aspart	Low cost
	Regular insulin	Aspart only available as 100units/mL
	Non-formulary Alternatives	Other Considerations
Regular U-500	Provider should be experienced in prescribing U500	
Insulin lispro U-100		
Insulin glulisine U-100		

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 27, 2015) using the search term insulin lispro 200. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

There are no clinical trials that evaluate efficacy of lispro U-200

Potential Off-Label Use

None

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	None
Contraindications	<ul style="list-style-type: none"> • During episodes of hypoglycemia • Hypersensitivity to insulin lispro or its excipients
Warnings/Precautions	<p>Never share lispro KwikPen between patients even if the needle is changed</p> <p>Do not transfer Lispro U-200 from the Humalog KwikPen to a syringe as overdosage and severe hypoglycemia can occur</p> <p>Hypoglycemia due to Medication Errors: Potential for mix-up between different types of insulin. Instruct patients to always check the insulin label before each injection</p> <p>As with other insulin products, there is a risk for hypoglycemia, hypersensitivity and allergic reactions, hypokalemia, and fluid retention/heart failure with concomitant use of thiazolidinediones.</p>
Safety Considerations	Same as for all rapid-acting insulin analogs

Risk Evaluation

Sentinel event advisories	! The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used. Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Lispro 200U/mL				Lispro 100U/mL
Humalog U-200	Humalog Humalog Mix 50/50, 75/25 Humira Humulin N Humulin R Novolog			

Other Considerations

Storage

Unopened not-in-use pens should be stored in a refrigerator (36-46°F). They are good until the expiration date. Not-in-use unopened pens stored at room temperature are good for 28days.

Open in-use pens should be stored at room temperature below 86°F (do not refrigerate) and must be used within 28 days or be discarded even if they still contain lispro.

For patients who require ≤ 20units/day, the pen will expire before it is empty

Excipients

The buffer has been changed from dibasic sodium phosphate (U-100) to tromethamine (U-200). The zinc ion content was increased from 0.0197mg/mL (U-100) to 0.046mg/mL (U-200).

Pharmacokinetics/Pharmacodynamics

The pharmacokinetics and pharmacodynamics of Lispro U-200 and Lispro U-100 were compared in healthy subjects (n=38) using euglycemic clamp method. This was an open-label, 20sequence, 4-period crossover, randomized 8-hour study. Patients received a single 20unit subcutaneous dose of either drug. The two formulations were found to be bioequivalent after a 20U subcutaneous injection in healthy subjects.

		Lispro U-200	Lispro U-100
Pharmacokinetics	Insulin AUC _(0-∞) (pmol·hr/L)	2360	2390
	Peak insulin concentration (pmol/L)	795	909
	Median time to max insulin concentration (h)	1.0	1.0
Pharmacodynamics	Glucose infused during clamp (g)	125	126
	Maximum glucose infusion rate (mg/min)	534	559
	Median (min, max) time to maximum effect (h)	2.8 (0.5-6.3)	2.4 (0.5-4.7)

Dosing and Administration

Administer within 15 minutes before a meal or immediately after a meal by subcutaneous injection of the abdominal wall, thigh, upper arm, or buttocks.

To avoid the risk of lipodystrophy, rotate the injection site within the same region from one injection to the next

Special Populations (Adults)

	Comments
Elderly	
Pregnancy	
Lactation	Information provided in package insert is based on lispro U100. There was no additional information specific to lispro U200.
Renal Impairment	
Hepatic Impairment	
Pharmacogenetics/genomics	None

Projected Place in Therapy

Insulin lispro 200units/mL might be tried for patients who have unexpected late low blood sugar from U-500.

References:

Product package insert for Humalog (5/2015)

de la Pena A, Seger M, Soon D, et al. Bioequivalence and comparative pharmacodynamics of insulin lispro 200 units/mL relative insulin lispro (Humalog) 100 units/mL. Clin Pharmacol Drug Develop DOI 10.1002/cpdd.221

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