New Medicine Assessment

Insulin Lispro (Lyumjev®▼) solution for injection for the treatment of diabetes mellitus in adults

Recommendation: Green (Restricted)

Conditions: Insulin Lispro (Lyumjev®) is recommended for the treatment of diabetes mellitus in adults who are suitable for Humalog® and their diabetes cannot be adequately managed with alternative formulary choices and at least one of the following applies:

- **Where the prescriber believes a faster onset of action would be beneficial to the patient**
- **Where a patient requires 'tight' control of blood sugar levels**
- **Where a patient has rapid post-meal increase in blood sugar levels**

Summary of supporting evidence:

- Lyumjev® treatment demonstrated consistently better PPG control compared to Humalog®. Studies in both T1D and T2D met 2 prespecified multiplicity objectives; when administered prior to the start of the meal, Lyumjev® was superior to Humalog® in controlling 1-hour and 2-hour PPG excursions during mixed meal tolerance test.
- Superior post prandial control offered by Lyumjev® use may benefit pregnant patients trying to achieve tighter post prandial glycaemic control in line with the NICE guideline for pregnancy.
- There was no overall difference in the risk of hypoglycaemic events between Humalog® and Lyumjev®.
- If pre-prandial dosing is not possible, Lyumjev® can be injected up to 20 minutes after the meal. However, the EMA advises that dosing of Lyumjev® should occur prior to meals if feasible, as postprandial glucose control and rate of hypoglycaemia are more beneficial in pre-prandial vs. postprandial administration
- As Lyumjev® is available at the same acquisition cost as Humalog®, no financial impact is expected.

Details of Review

Name of medicine (generic & brand name)**:**

Insulin Lispro (Lyumjev®▼)

Strength(s) and form(s):

100 units/mL solution for injection

Dose and administration:

Lyumjev® is a mealtime insulin for subcutaneous injection and should be administered zero to two minutes before the start of the meal, with the option to administer up to 20 minutes after starting the meal. [1]

Lyumjev® 100 units/mL is suitable for continuous subcutaneous insulin infusion (CSII) and is used for both the bolus and basal insulin requirement.

BNF therapeutic class / mode of action:

Insulins and anti-diabetic drugs/ rapid acting insulin

Licensed indication(s):

Treatment of diabetes mellitus in adults.

Proposed use (if different from, or in addition to, licensed indication above):

As per licensed indication.

Course and cost:

100iu/ml:

5 x 3ml cartridges=£28.31.
5 x 3ml KwikPen=£29.46.
5 x 3ml Junior KwikPen=£29.46.
1 x 10ml vial=£16.61.

200iu/ml:

5 x 3ml KwikPen=£58.92.

Costs based on MIMS list prices December 2020

Current standard of care/comparator therapies:

- Humalog® (insulin lispro)
- Fiasp® (insulin aspart) – has the closest profile to Lyumjev® in terms of rapid reduction in pre-prandial blood glucose
- NovoRapid® (insulin aspart)
- Apidra® (insulin glulisine)

Relevant NICE guidance:

NICE clinical guideline NG17 (Type 1 diabetes in adults: diagnosis and management August 2015) indicates that multiple daily injection basal-bolus insulin regimens should be the treatment of choice in all adults with type 1 diabetes in preference to non- basal-bolus insulin regimens (i.e. twice daily mixed, basal only or bolus only regimens).

For rapid-acting insulin NG17 states:

1.7.7 Offer rapid acting insulin analogues injected before meals, rather than rapid acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes.

1.7.8 Do not advise routine use of rapid acting insulin analogues after meals for adults with type 1 diabetes.

1.7.9 If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. [2]

NICE guideline NG28 (Type 2 diabetes in adults: management) July 2015 advises insulin-based treatment as an option if:

- Dual therapy with metformin and another oral drug has not continued to control HbA1c to below the patient's individually agreed threshold for intensification or
- Metformin is contraindicated or not tolerated and dual therapy with two oral drugs has not continued to control HbA1c to below the patient's individually agreed threshold for intensification.

Initially adult type 2 diabetic patients can be offered:

- NPH (isophane) insulin injected once or twice daily.
- Both NPH and short acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either:
    - separately or
    - as a pre-mixed (biphasic) human insulin preparation.

NG28 also states:

1.6.36 Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short acting insulin before meals (or a premixed [biphasic] insulin preparation).

1.6.37 Monitor adults with type 2 diabetes who are on pre mixed (biphasic) insulin for the need for a further injection of short acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. [2]

Background and context

The World Health Organisation defines diabetes as a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. [4]

Type 1 diabetes affects over 370,000 adults in the UK. Loss of insulin secretion results in high blood glucose and other metabolic and haematological abnormalities, which have both short-term and long-term adverse effects on health. Over years, type 1 diabetes causes tissue damage which, if not detected and managed early, can result in blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death. The risk of all of these complications is greatly reduced by treatment that keeps circulating glucose levels to as near normal as possible, reducing tissue damage. Complications can often be prevented by early detection and active management. [2]

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in hyperglycaemia. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

In 2018, over 3.4 million adults were diagnosed with diabetes, with prevalence rates of 6.8% in the United Kingdom. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family origin. It can occur in all age groups and is increasingly being diagnosed in children. [3]

Lyumjev® was identified for review following a request from a Diabetes Specialist Nurse in Morcambe Bay CCG. Lyumjev® is a novel formulation of insulin lispro (Humalog®) containing locally-acting excipients (citrate and treprostinil) to accelerate insulin lispro absorption. The concentration of active substance is identical to Humalog®, with the addition of two excipients, sodium citrate and treprostinil, which aim at accelerating the absorption at the site of injection by increasing blood vessel permeability (sodium citrate) and vasodilatation (treprostinil). [5]

Summary of evidence

Summary of efficacy data in proposed use:

The efficacy evaluation of Lyumjev®/ultra-rapid lispro (URLi) is based on three Phase 3 studies comparing Lyumjev® with Humalog®. PRONTO-T1D [6] and PRONTO-T2D [7] were randomized, parallel-design, double-blind, active controlled, treat-to-target trials that evaluated the safety and efficacy of URLi when administered as a prandial insulin as part of a (multiple dose injection) MDI regimen in adult patients with type 1 diabetes (T1D) and type 2 diabetes (T2D), respectively. PRONTO-Pump [8] was a 2-treatment, 2-period (6-week treatment each) crossover design trial that evaluated the safety and compatibility of URLi in the treatment of patients with T1D when administered via continuous subcutaneous insulin infusion pump (CSII) compared with Humalog®. [5]

Altogether 1944 patients with T1D or T2D received study drug (Lyumjev® or the active comparator Humalog®) in the Phase 3 studies, of which 1165 received Lyumjev®. Patients were excluded from studies if there were safety issues (with labile diabetes control such as frequent hypoglycaemic events or ketoacidosis requiring emergency treatment, and of patients with hypoglycaemia unawareness) or inappropriate combination of medications in T2D patients

(GLP1 receptor agonists, pramlintide or thiazolidinediones). Both PRONTO-T1D and PRONTO-T2D trials included an 8-week lead-in period; a 12-week intensive titration period; and a 26-week controlled period assessing non-inferiority based on change in HbA1c of Lyumjev® compared with Humalog® (primary objective). [5]

PRONTO-T1D study

The PRONTO-T1D was conducted with three arms: Lyumjev® and Humalog® administered immediately (0-2 minutes) prior to each meal in a double-blind manner, and as third treatment group Lyumjev® was administered 20 minutes after the start of a meal open-label, as it was not possible to blind this treatment group with different injection timing. The primary endpoint was change from baseline glycated haemoglobin (HbA1c) to 26 weeks (non-inferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions after a meal test. Both mealtime and post-meal URLi demonstrated non-inferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi −0.08% [CI95% −0.16; 0.00] and for post-meal URLi +0.13% (CI95% 0.04; 0.22), with a significantly higher endpoint HbA1c for post-meal URLi versus lispro (P = 0.003). Mealtime URLi was superior to lispro in reducing 1- and 2-hour PPG excursions during the meal test: ETD −1.55 mmol/L (CI95% −1.96; −1.14) at 1 hour and − 1.73 mmol/L (CI95% −2.28, −1.18) at 2 hours (both P < 0.001). The rate and incidence of severe, documented and postprandial hypoglycaemia (<3.0 mmol/L) was similar between treatments, but mealtime URLi demonstrated a 37% lower rate in the period >4 hours after meals (P = 0.013). [6]

PRONTO-T2D study

The PRONTO-T2D study compared Lyumjev® and Humalog®, both administered immediately prior to meals. Patients could continue metformin and/or a sodium–glucose cotransporter 2 inhibitor. The endpoints of the study were identical to those of the PRONTO-T1D study. HbA1c improved for both URLi and lispro, and noninferiority was confirmed: ETD 0.06% (CI95% -0.05; -0.16). Mean change in HbA1c was -0.38% for URLi and -0.43% for lispro, with an end-of-treatment HbA1c of 6.92% and 6.86%, respectively. URLi was superior to lispro in controlling 1- and 2-h PPG excursions: 1-h ETD, -0.66 mmol/L (95% CI -1.01, -0.30); 2-h ETD, -0.96 mmol/L (-1.41, -0.52). Significantly lower PPG excursions were evident from 0.5 to 4.0 h post meal with URLi treatment. There were no significant treatment differences in rates of severe or documented hypoglycaemia (<3.0 mmol/L). [7]

PRONTO-PUMP study

The PRONTO-PUMP study on patients with T1D using continuous subcutaneous insulin infusion (CSII) via external insulin pump was primarily designed to confirm safety and compatibility of Lyumjev® for use in an insulin pump. The study was not powered to demonstrate non-inferiority or superiority for efficacy. However secondary analysis of continuous glucose monitoring data demonstrated a trend toward improved glycaemic control with URLi treatment during the daytime and 24-h period with increased time in target range.

Summary of safety data:

A total of 1165 patients received Lyumjev® in the three Phase 3 studies. Of these patients, 921 received Lyumjev® as multiple daily injections for at least 180 days, and 33 received Lyumjev® via pump for at least 42 days. The active substance in Lyumjev® (insulin lispro) has been approved for use for over 20 years. Due to the negligible systemic exposure following SC and IV administration of pharmacological active excipients (most notably treprostinil), additional studies of their safety have not been included in the safety assessment.

The primary difference in adverse events between an ultra-rapid formulation and rapid formulation of insulin lispro is the time to post-dose hypoglycaemia events. In both T1D and T2D patients, the hypoglycaemia events occurred more rapidly with Lyumjev® after the meals compared to Humalog®; in Humalog® groups, the hypoglycaemia events occurred closer to 4 h

post-meal and in Lyumjev® groups starting right after the meals. This is in line with the nature of the new fast-acting product. In T2D, the incidence and rate of documented hypoglycaemia was slightly higher with Lyumjev®. The rate of severe hypoglycaemia did not differ between Lyumjev® and Humalog®.

The full list of adverse events included in the Summary of Product Characteristics are tabulated below [1]:

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to ≤1/10)	Uncommon (≥1/1000 to ≤1/100)	Not known
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders			Lipodystrophy	Cutaneous amyloidosis
			Rash	
			Pruritus	
General disorders and administration site conditions		Injection site reactions	Oedema	
		Allergic reactions		

Lyumjev® is contraindications in hypoglycaemia and in patients with Hypersensitivity to the active substance or to any of the excipients. Precautions for the use of Lyumjev® are in line with other insulin products including warnings relating to hypoglycaemia, hyperglycaemia, injection technique, dose adjustments and insulin pump failures.

Strengths and limitations of the evidence:

Strengths [5]

- In the two Phase 3 multiple-daily-injection regimen studies in TD1 and TD2 patients Lyumjev® was non-inferior compared to Humalog® for change in HbA1c from baseline to Week 26.
- Lyumjev® treatment demonstrated consistently better PPG control compared to Humalog®. Studies in both T1D and T2D met 2 prespecified multiplicity objectives; when administered prior to the start of the meal, Lyumjev® was superior to Humalog® in controlling 1-hour and 2-hour PPG excursions during mixed meal tolerance test.
- Superior post prandial control offered by Lyumjev® use may benefit pregnant patients trying to achieve tighter post prandial glycaemic control in line with the NICE guideline for pregnancy.
- There was no overall difference in the risk of hypoglycaemic events between Humalog® and Lyumjev®.
- If pre-prandial dosing is not possible, Lyumjev® can be injected up to 20 minutes after the meal. However, the EMA advises that dosing of Lyumjev® should occur prior to meals if feasible, as postprandial glucose control and rate of hypoglycaemia are more beneficial in pre-prandial vs. postprandial administration.

Limitations [5]

- In T2D, the benefits achieved by using Lyumjev® preprandially vs. Humalog® preprandially are not as strong as in T1D.
- There was no comparison to Humalog® administered 15 minutes prior to meals (only immediately prior to meals), which would be the optimal dose regarding the time-action

profile of Humalog®. In addition, no comparison is available for Humalog® administered post-meal.

- There was a slight difference in HbA1c in favour of Lyumjev® in the PRONTO-T1D study, however, the secondary endpoint of superiority in terms of HbA1c was not met. In T2D patients, HbA1c was also similar in both groups. These results might be interpreted as an argument against the importance of postprandial control to overall glycaemic burden. However, no marked changes in HbA1c can be expected in treat-to-target studies.
- It is uncertain if the name of the Lyumjev® KwikPen Junior presentation carries a risk for off-label use in paediatric population, since "Junior" might be associated with paediatric patients.
- The frequency of local reactions at injection and infusion site increased markedly, about 10-fold in patients administered Lyumjev® vs. Humalog®. On the other hand, most reactions were mild to moderate and transient.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

It is uncertain if the name of the Lyumjev® KwikPen Junior presentation carries a risk for off-label use in paediatric population, since "Junior" might be associated with paediatric patients.

Prescribers should also be aware that Lyumjev® is available in prefilled pens in two strengths (100iu/ml and 200iu/ml). To avoid medication errors between Lyumjev® and other insulins, patients need to always check the insulin label before each injection.

Lyumjev® should not be used by patients with visual impairment without help of a trained person.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Insulin lispro (Lyumjev®) 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Insulin lispro (Lyumjev®) KwikPen/ KwikPen Junior 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£29.46	£144 - £287
Insulin aspart (Fiasp®) FlexTouch 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£30.60	£149 - £298
Insulin aspart (Fiasp®) Penfill 100unit/ml cartridges	Dosage according to requirements. Assuming	£28.31	£138 - £276

	total daily dose of 20-40 units		
Insulin lispro (Humalog®) 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Insulin lispro (Humalog®) KwikPen 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£29.46	£144 - £287
Insulin glulisine (Apidra®) 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.30	£138 - £276
Insulin glulisine (Apidra®) SoloStar 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.30	£138 - £276
Insulin aspart (NovoRapid®) FlexPen 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£30.60	£149 - £298
Insulin aspart (NovoRapid®) FlexTouch 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£32.13	£157 - £313
Insulin aspart (NovoRapid®) Penfill 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Costs based on MIMS list prices December 2020. This table does not imply therapeutic equivalence of drugs or doses.			

References

[1] Electronic Medicines Medicines Compendium, "Summary of Products Characteristics Lyumjev 100 units/mL KwikPen solution for injection in pre-filled pen," Eli Lilly Company Limited, August 2020. [Online]. Available: https://www.medicines.org.uk/emc/product/11536/smpc. [Accessed December 2020].

[2] National Institute for Health and Care Excellence, "Type 1 diabetes in adults: diagnosis and management (NG17)," August 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations. [Accessed December 2020].

[3] National Institute for Health and Care Excellence, "Type 2 diabetes in adults: management," December 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng28. [Accessed October 2018].

[4] World Health Organisation (WHO), "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1 diagnosis and classification of diabetes mellitus," WHO/NCD/NCS 99.2, Geneva, 1999.

[5] European Medicines Agency, "Public Assessment Report Liumjev EMEA/H/C/005037/0000," January 2020. [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/liumjev-epar-public-assessment-report_en.pdf. [Accessed December 2020].

[6] L Klaff et al, "Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with tyoe 1 diabetes: Results from the 26-week PRONTO-T1D study," *Diabetes Obes Metab,* vol. 22, pp. 1799-1807, 2020.

[7] T Blevins et al, "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,* vol. 43, pp. 2991-2998, 2020.

[8] B Bode et al, "Compatibility and Safety of Ultra Rapid Lispro with Continuous Subcutaneous Insulin Infusion in Patients with Type 1 Diabetes: PRONTO-Pump Study," *Diabetes Technology & Therapeutics,* vol. 23, no. 1, p. DOI: 10.1089/dia.2020.0224, 2020.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Produced by:
Midlands and Lancashire Commissioning Support Unit, 2021