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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Dulaglutide for Type 2 diabetes

NIHRIO ID	23961	**NICE ID**	10660
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	662850

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Dulaglutide is in clinical development for the treatment of children and adolescents with type 2 diabetes mellitus (T2DM). T2DM is a lifelong condition that develops when the body becomes resistant to, or does not produce enough, insulin – a hormone produced in the pancreas. Insulin is needed for glycaemic control (controlling the amount of sugar in the blood). A lack of insulin, or resistance to insulin in T2DM patients causes blood sugar levels to become too high. If blood sugar remains high over a long period of time this can result in serious complications. Pharmacotherapeutic options for youth with T2DM are limited at this time. Therefore, there is a need to develop new treatment options that are effective in reducing blood sugar levels in T2DM patients.

Subcutaneous dulaglutide activates the receptor for glucagon-like peptide 1 (GLP-1). When the blood sugar is at higher levels, dulaglutide causes the pancreatic cells to release insulin and other processes that regulate blood sugar. If licensed, dulaglutide will provide an additional treatment option to improve glycaemic control in children and adolescents with T2DM.

PROPOSED INDICATION

Pediatric patients (10 years to 17 years) with T2DM.[1]

TECHNOLOGY

DESCRIPTION

Dulaglutide (LY-2189265; Trulicity) is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. The molecule consists of 2 identical disulfide-linked chains, each containing a modified human GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker. The GLP-1 analog portion of dulaglutide is approximately 90% homologous to native human GLP-1 (7-37). Native GLP-1 has a half-life of 1.5 - 2 minutes due to degradation by DPP-4 and renal clearance. In contrast to native GLP-1, dulaglutide is resistant to degradation by DPP-4, and has a large size that slows absorption and reduces renal clearance. These engineering features result in a soluble formulation and a prolonged half-life of 4.7 days, which makes it suitable for once-weekly subcutaneous administration. In addition, the dulaglutide molecule was engineered to prevent the Fcγ receptor-dependent immune response and to reduce its immunogenic potential.[2]

Dulaglutide exhibits several antihyperglycaemic actions of GLP-1. In the presence of elevated glucose concentrations, dulaglutide increases intracellular cyclic AMP (cAMP) in pancreatic beta cells leading to insulin release. Dulaglutide suppresses glucagon secretion which is known to be inappropriately elevated in patients with T2DM. Lower glucagon concentrations lead to decreased hepatic glucose output. Dulaglutide also slows gastric emptying.[2]

In the phase III trial (NCT02963766), two doses of dulaglutide will be administered via subcutaneous (SC) injection at a dose of 0.75mg/week and 1.5mg/week in a 26-week double-blind period, followed by a 26-week open-label extension.[1,3]

INNOVATION AND/OR ADVANTAGES

T2DM is increasing in children and young people, it is also a severe, progressive form of the condition. It is associated with greater insulin resistance and more rapid deterioration of beta cell function decline than T2DM in adults.[4]
T2DM in the paediatric population is managed with either metformin, insulin and/or lifestyle and dietary changes.[5] In adults dulaglutide is a GLP-1 receptor agonist that has had a successful head-to-head trial showing noninferiority to liraglutide and studies have demonstrated that dulaglutide is more effective than other antidiabetic agents, by reducing the HbA1c by close to or greater than 1%. It also requires once weekly dosing compared with other agents' once-daily dosing, making it more convenient for patients.[6] If approved, dulaglutide will provide an additional treatment option for children and adolescents with T2DM.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Dulaglutide is licensed in the UK for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise:[2]

- As a monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- In addition to other medicinal products for the treatment of diabetes.

Very common adverse events (frequency ≥ 1/10) of dulaglutide as a monotherapy include: hypoglycaemia, nausea, diarrhoea, vomiting, abdominal pain.[2]

Dulaglutide is also in phase II clinical development for the treatment of cystic fibrosis, primary polydipsia, smoking cessation and sexual functioning.[8]

PATIENT GROUP

DISEASE BACKGROUND

T2DM is an impairment in the way the body regulates and uses sugar (glucose) as a fuel. This long-term (chronic) condition results in too much sugar circulating in the bloodstream. In T2DM the pancreas does not produce enough insulin — a hormone that regulates the movement of sugar into cells — and cells respond poorly to insulin and take in less sugar. T2DM used to be known as adult-onset diabetes, but both type 1 and type 2 diabetes can begin during childhood and adulthood. Type 2 is still more common in older adults, but the increase in the number of children with obesity has led to more cases of T2DM in younger people.[9]

The exact cause of T2DM is unknown but family history and genetics appear to play an important role. Inactivity and excess fat — especially fat around the belly — also seem to be important factors.[10] Compared with people aged 40 and over, young people with T2DM are more likely to be: female, of a minority ethnic background, living in an area of social deprivation and classified as overweight or obese.[11]

T2DM in children may develop so gradually that there are no noticeable symptoms. Sometimes, the disorder is diagnosed during a routine check-up. Other children might experience increased thirst and frequent urination, fatigue, blurry vision, darkened areas of skin and weight loss.[10]

T2DM can affect nearly every major organ in a child's body, including the blood vessels, nerves, eyes and kidneys. The long-term complications of T2DM develop gradually over many years. Eventually, diabetes complications may be disabling or even life-threatening. Complications of T2DM include: high blood pressure, high cholesterol, heart and blood vessel disease, stroke, non-alcoholic fatty liver disease, kidney disease, blindness and amputation.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Between April 2015 and April 2016, the UK incidence of T2DM was estimated to be 0.72 per 100,000 children (aged 0-16) years per year.[5] The National Paediatric Diabetes Audit in 2019-20 found there were 122,780 children and young adults under the age of 40 years with T2DM in England; of whom 1,560 (around 1.3 per cent) were under the age of 19 years.[11]

The hospital episode statistics (HES) for diagnosis in England in 2019-2020, recorded a total of 204 finished consultant episodes (FCEs) for primary diagnosis of T2DM (ICD-10 E11.0) in patients aged under 19 years.[12]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

T2DM in youth should be managed by a multidisciplinary team consisting of a physician/other medical provider with expertise in diabetes, dietitian, nurse educator, mental health professional, and exercise specialists, if possible. The overarching goals of management of youth with T2DM are to achieve and subsequently maintain glycaemic control, identify and manage associated comorbid conditions, and ultimately prevent microvascular and macrovascular complications of diabetes. Management includes lifestyle changes like physical activity goals and nutritional recommendations and certain pharmacological interventions.[13]

CURRENT TREATMENT OPTIONS

NICE recommends standard-release metformin to children and young people with T2DM.[7]

PLACE OF TECHNOLOGY

If licensed, subcutaneous dulaglutide will provide an additional treatment option to improve glycaemic control in children and adolescents with T2DM.

CLINICAL TRIAL INFORMATION

Trial	**AWARD-PEDS;** NCT02963766, 2016-000361-22; A Randomized, Double-Blind Study With an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide With Placebo in Pediatric Patients With Type 2 Diabetes Mellitus (AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study) **Phase III** - Active, not recruiting **Location(s):** 3 EU countries, UK, USA and other countries **Primary completion date:** January 2022
Trial design	Randomised, parallel assignment and double-blind.
Population	N = 154, type 2 diabetes, treated with diet and exercise, with or without metformin and/or basal insulin, aged 10 years to 17 years.
Intervention(s)	Dulaglutide given subcutaneously.
Comparator(s)	Placebo given subcutaneously.
Outcome(s)	Primary outcome; - Change from baseline in Hemoglobin A1c (HbA1c) [Time frame: baseline, week 26] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of 4 x 1.5mg/0.5ml solution for injection pre-filled pens of dulaglutide is £73.25.[14]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015.
- NICE quality standard. Diabetes in children and young people (QS125). July 2016.
- NICE evidence summary. Type 2 diabetes: dulaglutide (ESNM59). June 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Endocrinology and Diabetes. E03/S/e.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Diabetes – type 2. 2021.[15]
- Children and Young People's West Midlands Diabetes Network. Diagnosis and management of Type 2 Diabetes (T2DM) in Children and Young People (CYP): Clinical Practice Guideline. June 2019.[16]
- International society for paediatric and adolescent diabetes (ISPAD). ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth. July 2018.[17]

ADDITIONAL INFORMATION

REFERENCES

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