Drug Information Bulletin

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Content

- ***Editorial***
- ***New Drug: Dulaglutide for type 2 diabetes***
- ***Safety issues of Fluoroquinolones: DCGI directed to mention various cautions in the label/Package insert/ Promotional literature of fluoroquinolones***

Editorial

Wishing you all a happy "Deepavali"!

A new publication from the Promoting the Quality of Medicines (PQM) program, which is funded by the USAID and implemented by the U.S. Pharmacopeia (USP) reviews key regulatory challenges in LMICs, which identified that though much progress has been made globally in strengthening regulatory systems, serious challenges remain to ensure the quality and safety of medicines, particularly in LMICs. MRAs in LMICs often have limited capacity and/or insufficient resources to carry out the range of critical regulatory functions effectively. WHO estimates that at least 30 percent of MRAs globally are operating with limited capacity to perform core regulatory functions. In Africa, more than 90 percent of MRAs are operating with minimal capacity. Assessments in multiple countries indicate inconsistent, outdated, and sometimes nonexistent legislative frameworks and policies that incapacitate an MRA and prevent it from operating effectively. Complicating this issue is the overall heterogeneity of regulatory frameworks, policies, and standards across LMICs, which can slow down the process of market authorization for new medicines and hinder their access. The limitations in human and financial resources often limit regulatory functions and can create inefficiencies in regulatory processes. As a result, MRAs in LMICs often face significant backlogs of medicines registration applications and very meager resources to effectively carry out inspection, quality control, and post-marketing surveillance activities. Ineffective or absent governance mechanisms and information management systems contribute to a lack of accountability and transparency and the mismanagement of regulatory information and data.

In contrary to this, Indian drug legislation is being updated regularly and the regulatory framework is strengthened regularly. As a result WHO declares that CDSCO is a functional MRA.

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New Drug: Dulaglutide for type 2 diabetes

Approved indication: type 2 diabetes
Trulicity (Eli Lilly)
pre-filled pens and syringes containing
1.5 mg/0.5 mL solution

When drug treatment is needed for type 2 diabetes, patients are usually prescribed metformin. If this does not control blood glucose, a second drug may need to be added.[1] This includes the glucagon-like peptide-1 (GLP-1) analogues, such as exenatide and liraglutide. Like these drugs, dulaglutide acts as an agonist at the GLP-1 receptor. It therefore increases the secretion of insulin when glucose concentrations are high.

Dulaglutide is a genetically engineered protein. It therefore has to be given by subcutaneous injection. The way the molecule is engineered slows its absorption and clearance. Peak plasma concentrations are reached in 48 hours and the half-life is 4.7 days. This makes dulaglutide suitable for once-a-week injections. It takes 2–4 weeks to reach a steady state. The molecule is catabolised and no dose adjustment is required for hepatic impairment or mild–moderate kidney impairment.

There have been multiple studies of dulaglutide as monotherapy and in combination with other drugs. Its approval in Australia is based on five main trials.[2-6] Although the recommended weekly dose is 1.5 mg, these AWARD trials also studied 0.75 mg.

Monotherapy

Dulaglutide was compared with metformin in a double-blind trial involving 807 patients with type 2 diabetes of less than five years duration. At the start of the AWARD-3 study the mean concentration of glycated haemoglobin (HbA1c) was 59.6 mmol/mol (7.6%). After 26 weeks this had reduced by 8.5 mmol/mol (0.78%) with dulaglutide 1.5 mg and by 6.1 mmol/mol (0.56%) with metformin. A target HbA1c concentration below 53 mmol/mol (7%) was achieved by 62% of the patients taking dulaglutide and 54% of those taking metformin. These statistically significant advantages for dulaglutide 1.5 mg were still present after 52 weeks of treatment.[2]

Added to metformin

In the AWARD-5 trial, 1098 patients treated with metformin were randomised to add dulaglutide, sitagliptin 100 mg daily or placebo. After 26 weeks the patients taking placebo changed to sitagliptin. At the start of the study the mean HbA1c was 65 mmol/mol (8.1%). After 26 weeks this reduced by 13.3 mmol/mol (1.22%) with dulaglutide 1.5 mg, 6.7 mmol/mol (0.61%) with sitagliptin and 0.3 mmol/mol (0.03%) with placebo. The reductions baseline at 52 weeks were 12 mmol/mol (1.1%) for dulaglutide and 4.3 mmol/mol (0.39%) for sitagliptin. Dulaglutide therefore had a significant advantage over sitagliptin. A target concentration under 53 mmol/mol (7%) was achieved by 58% of patients injecting dulaglutide and 33% of those taking sitagliptin.[3]

Added to metformin and a thiazolidinedione

Patients in the AWARD-1 trial were stabilised on a combination of metformin and pioglitazone. The 976 patients were then randomised to have weekly injections of dulaglutide or exenatide. There was also a group of patients who injected a placebo for 26 weeks then switched to dulaglutide. From a mean baseline of 65 mmol/mol (8.1%), the HbA1c had fallen by 16.5 mmol/mol (1.51%) with dulaglutide 1.5 mg and by 10.8 mmol/mol (0.99%) with exenatide at 26 weeks. The reduction in the placebo group was 5 mmol/mol (0.46%). At 52 weeks the reduction from baseline was statistically significantly greater with dulaglutide than exenatide (14.9 vs 8.8 mmol / mol (1.36% vs 0.89%)). The goal of an HbA1c concentration below 48 mmol / mol (6.5%) was achieved by 57% of the dulaglutide group and 35% of the exenatide group.[4]

Added to metformin and a sulfonylurea

Dulaglutide has been compared to insulin when treatment with metformin and glimepiride has been insufficient to control type 2 diabetes. In the open-label AWARD-2 trial 810 patients with an average HbA1c of 65–66 mmol/mol (8.1–8.2%) were randomised to inject dulaglutide weekly or insulin glargine daily. After 52 weeks the HbA1c had reduced by 11.8 mmol/mol (1.08%) with dulaglutide 1.5 mg and 6.9 mmol/mol (0.63%) with insulin glargine. This gave dulaglutide a statistical advantage. There was also a significant difference in the proportion of patients who achieved a target HbA1c below 53 mmol/mol (7%) (53.2% dulaglutide, 30.9% insulin). The statistical superiority of dulaglutide 1.5 mg over insulin was still present after 78 weeks of treatment.[5]

The open-label AWARD-4 trial involved 884 patients who were using insulin lispro with or without metformin. They were randomised to receive weekly dulaglutide or a bedtime injection of insulin glargine. From a baseline concentration of 68.95 mmol/mol (8.46%), HbA1c reduced by 17.93 mmol/mol (1.64%) after 26 weeks with dulaglutide 1.5 mg. With insulin glargine it reduced by 15.41 mmol/mol (1.41%) from a baseline of 69.72 mmol/mol (8.53%). This statistically significant difference was still present at 52 weeks. At that time, 59% of the patients injecting dulaglutide 1.5 mg had an HbA1c below 53 mmol/mol (7%) compared with 49% of those injecting insulin glargine.[6]

Safety

In studies lasting up to 104 weeks 8.4% of the patients injecting dulaglutide discontinued it because of adverse effects. Nausea, vomiting and diarrhoea are very common, particularly at the start of therapy. Pancreatitis is a possibility, but enzyme concentrations can be unhelpful for making the diagnosis as they rise during treatment with dulaglutide.

Hypoglycaemia can occur particularly in patients who are also taking insulin or a sulfonylurea. A meta-analysis of 12 trials of dulaglutide reported that with monotherapy 7.8% of patients developed hypoglycaemia compared with 10.6% of those in control groups.[7] In the study of patients taking metformin and glimepiride (AWARD-2), 55.3% of those given dulaglutide for 52 weeks developed hypoglycaemia compared with 69.1% of those who added insulin glargine. This difference was significant.[5]

The meta-analysis reported that dulaglutide reduced body weight less than metformin, but more than sitagliptin, exenatide and insulin glargine.[7] Across the studies the reduction from baseline was 0.35–2.88 kg.

Dulaglutide increases the heart rate and slightly lowers systolic blood pressure. It is also associated with atrioventricular block. The risk of cardiovascular events does not appear to differ from that of control treatments.

Some patients develop antibodies to dulaglutide. This does not appear to make them more prone to hypersensitivity reactions.

Place in therapy

As the clinical outcomes for some of the newer drugs for type 2 diabetes are not yet clear, the optimum combination is uncertain.[1] If a GLP-1 analogue is selected, there are few differences between them. Dulaglutide appears to have a greater effect on HbA1c than exenatide[4] and is non-inferior compared to liraglutide.[8] Although the absolute differences are small, dulaglutide appears to reduce weight more than exenatide,[4] but less than liraglutide.[8] As liraglutide is given daily, patients who want to minimise injections may prefer weekly dulaglutide.

References

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Status in India: A few brands are available in Indian market two of which are-
Trulicity: Dulaglutide 1.5 mg/0.5ml Rs. 2499
Aplevant: Dulaglutide 1.5 mg/0.5ml Rs. 2499

Safety issues of Fluoroquinolones: DCGI directed to mention various cautions in the label/Package insert/ Promotional literature of fluoroquinolones

As per the recent report fluoroquinolones may cause significant decreases in blood sugar and certain mental health side effects. The said report was considered by the CDSCO and directed the manufacturers of fluoroquinolones to mention following cautions in the label/Package insert/Promotional literature of the drugs.

1. The label of the product should mention following caution:
   This drug may cause low blood sugar and mental health related side effects.
2. Package insert and promotional literature should mention the details as follows:
   "The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:
   - Disturbances in attention
   - Disorientation
   - Agitation
   - Nervousness
   - Memory impairment
   - Serious disturbances in mental abilities called delirium."