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## 1. Linagliptin: An overview

Linagliptin is the most advanced investigational compound for the treatment of type 2 diabetes within the Boehringer Ingelheim diabetes portfolio. It belongs to the class of dipeptidyl peptidase (DPP)-4 inhibitors and is being developed as an oral once-daily tablet. In clinical studies to date, linagliptin has been shown to:<sup>1-6</sup>

- provide significant, sustained and clinically meaningful improvements in blood glucose control
- have an excellent safety and tolerability profile, and low risk of hypoglycaemia
- not cause weight gain
- not require dose adjustment, irrespective of concomitant disease or co-medication, even in patients with renal impairment (linagliptin has a primarily non-renal route of excretion)
- have a once-daily dosing regimen as a convenient small tablet which can be taken time and food independent

## 2. DPP-4 Inhibitors: A novel class of treatment in type 2 diabetes

DPP-4 inhibitors represent an innovative approach to type 2 diabetes treatment with a unique mechanism of action compared to other classes in this therapeutic area.

By binding to the DPP-4 enzyme, they inhibit the breakdown of the two incretin hormones, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP).<sup>7</sup> GLP-1 and GIP are naturally occurring hormones, which are released by the gut after meals and target the pancreas by increasing glucose-dependent insulin secretion and suppressing glucagon secretion. DPP-4 inhibitors increase the GLP-1 plasma concentrations within the physiological range in contrast to injectable GLP-1 mimetics which have supra-physiological plasma levels and are associated with an increased GI side-effect rate, such as nausea and vomiting.

The inhibition of DPP-4 is beneficial for type 2 diabetes patients to control blood glucose levels, a primary goal of type 2 diabetes management.<sup>8</sup> A dose-finding period (up-titration period) at the beginning of therapy is not needed when treating with a DPP-4 inhibitor. This is because of their rapid mode of action and the fact that their favourable tolerability profile does not cause nausea and vomiting and has a low risk of drug-drug interactions. This makes them appropriate for monotherapy or as add-on to existing treatment regimens.<sup>8</sup>

### 3. Linagliptin: Profile and clinical trials programme

#### Linagliptin: Profile<sup>1-6</sup>

The DPP-4 inhibitor linagliptin, an investigational compound from Boehringer Ingelheim research currently in phase III clinical development, reversibly binds to the DPP-4 enzyme.

Results from the phase III clinical trials programme consistently support findings from earlier linagliptin investigational studies. In phase III data analysed to date, linagliptin provided significant, clinically meaningful and sustained improvements in glycaemic control, with an incidence of adverse events similar to placebo and an excellent tolerability profile.<sup>1-6</sup> In addition, linagliptin has been shown to be weight neutral and, importantly, there was no increased risk of hypoglycaemia attributed to linagliptin use in monotherapy or combination therapy with metformin or pioglitazone.<sup>1-6</sup>

Further, linagliptin is to date the only DPP-4 inhibitor that has a primarily non-renal route of excretion (only approximately five percent is renally excreted).<sup>9</sup> Data to date suggest that linagliptin would not need dose adjustment in patients with type 2 diabetes, regardless of the degree of renal impairment.<sup>10</sup>

#### Linagliptin: Clinical trials programme<sup>1-6</sup>

The phase III clinical trials programme evaluates the safety, efficacy and tolerability of linagliptin alone and in combination with several commonly used diabetes treatments including metformin, sulfonylureas and thiazolidinediones (TZDs). The overall linagliptin phase III clinical trials programme includes more than 5,000 patients, several hundreds of them with different stages of renal impairment, as well as two independent longer term studies and investigations specifically into the safe and efficacious use of linagliptin in type 2 diabetes patients with mild, moderate and severe renal impairment.

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