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32-country study shows that type 2 diabetes drug is clinically effective for long-term use

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An extended trial of a drug for people with type 2 diabetes has confirmed that the oral DPP-4 inhibitor linagliptin is a safe and effective means of lowering glucose levels for up to 102 weeks, either on its own or in combination with other selected oral anti-diabetic medication.

The 32-country study, published in the August issue of *IJCP*, the International Journal of Clinical Practice, followed 2,121 individuals who had taken part in four previous 24-week randomised, double-blind, placebo controlled trials, in order to monitor them for a further 78 weeks.

Those subjects who had previously received linagliptin (1,532) continued to do so and those who had received the placebo during the earlier trials (589) were also given the drug during the 78-week trial extension.

The participants who took part in the extended trial came from 231 sites in 32 countries: Argentina, Austria, Belgium, Canada, China, Croatia, the Czech Republic, Finland, Germany, Greece, Hungary, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, the Philippines, Poland, Romania, Russia, Slovakia, Spain, Sweden, Taiwan, Thailand, Ukraine, the United Kingdom and the United States.

"Initial 24-week trials showed that linagliptin, either on its own or with other glucose-lowering agents, was effective in improving glycaemic control without weight gain or an independent increased risk of

hypoglycaemia (reduced blood sugar levels)" says co-author David R Owens, Professor Emeritus, Centre for Endocrinology and Diabetes Sciences at Cardiff University, Wales, UK.

"Linagliptin works by blocking the action of DPP-4, an enzyme that destroys the hormone GLP-1, which helps the body produce more insulin when it is needed." Linagliptin was administered orally once a day in all cases, either on its own, or in combination with metformin or metformin plus a sulphonylurea or pioglitazone.

Key findings of the extended study included:

- The study participants had an average age of 57.5 years, 75% were younger than 65 years, 51.8% were male and 52.5% had been diagnosed more than five years ago.
- The majority had a body mass index of less than 30 kg/m2 (62.4%), a normal or mildly impaired kidney function (95.6%) and glycated hemoglobin levels of less than 8% (71.2%). The mean baseline glycated haemoglobin and fasting plasma glucose levels were significantly lower in those subjects who had received linagliptin rather than the placebo in the previous 24-week trials.
- 1,880 people (88.6%) completed the trial. The main reasons for discontinuing were adverse side effects (3.7%), refusal to continue medication (2.6%) and lack of therapeutic effect (1.1%).
- 1,718 subjects (81%) reported at least one adverse episodes during the extension phase. The highest incidence were in people receiving the combination of linagliptin plus metformin and a sulphonylurea (84.2%), followed by those receiving linagliptin plus metformin (81.6%). When linagliptin was taken on its own, the adverse side effects rate was lower at 78.8%, similar to those

on linagliptin plus pioglitazone (76%).

- Most adverse side effects were mild or moderate and the incidence of severe adverse side effects was low at 3.8%, with 3.4% discontinuing the drug as a result. Overall, 14.3% of participants experienced drug-related adverse incidents.
- The investigators determined that 13.9% of participants experienced hyploglycaemic (low blood sugar) events and that about half of these (6.9%) were drug-related.
- The highest level of drug-related hypoglycaemic events occurred in persons receiving metformin with a sulophonylurea (11%), with much lower rates for those receiving linagliptin plus metformin (2.1%), lingaliptin on its own (0.5%) and lingaliptin plus pioglitazone (0.2%).
- Serious adverse events were reported in 9.9% of the trial subjects, with eight deaths reported during the study period. However, these were not related to the drug.
- Long-term lingagliptin use was not associated with a clinically relevant change in body weight, with individuals previously on the drug losing an average of 0.03kg and those previously on the placebo gaining an average of 0.47 kg.

"This is the largest data set of long-term clinical evidence for linagliptin to date" concludes Professor Owens.

"Findings from the 78-week open-label extension involving 2,121 people with type 2 diabetes demonstrate sustained glycaemic control for up to 102 weeks treatment duration.

"They also provide evidence that supports the efficacy and tolerability profile seen in previously reported 24-week studies. Therefore this extension study shows that linagliptin is an effective and well tolerated therapy for the long-term management of type 2 diabetes."

More information: Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week phase III trials followed by a 78-week open-label extension. Gomis et al. IJCP. 66.8, pp731. (August 2012). doi: 10.1111/j.1742-1241.2012.02975.x

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