

Company Announcement

28 June 2009

Novo Nordisk insulin analogues have proven safety profiles

On Friday 26 June, *Diabetologia*, the journal of the European Association for the Study of Diabetes (EASD) published online data from four studies relating to a possible link between a long-acting insulin analogue, insulin glargine, and cancer¹. As a basis for such a possible link, an accompanying editorial explains that certain insulin analogues have a structure making them more likely to bind to the IGF-1 receptor which is known to be involved in promoting tumour growth².

Novo Nordisk markets three insulin analogues, Levemir® (insulin detemir), a long-acting basal insulin analogue, NovoRapid®/NovoLog® (insulin aspart), a short-acting insulin analogue, and NovoMix®/NovoLog® Mix 70/30 (biphasic insulin aspart). To avoid unnecessary speculation about whether Novo Nordisk insulin analogues may be associated with an increased risk of cancer, the company wishes to highlight the following:

- For the past 20 years, all Novo Nordisk insulin analogues have been tested for IGF-1 receptor binding in the early research phase and only insulins with a binding ratio between the insulin and IGF-1 receptors similar to, or better than, that of human insulin have been accepted for further development³.
- Studies on receptor binding and cell growth together show that insulin aspart, the insulin analogue present in NovoRapid®/NovoLog® and NovoMix®/NovoLog® Mix 70/30 has an *in vitro* safety profile that is identical to that of human insulin^{3,4}.
- Studies on receptor binding have shown that Levemir® in comparison to human insulin has a relative affinity to the IGF-1 receptor which is equal to or slightly lower than to the insulin receptor^{4,5}. Levemir® distinguishes itself from insulin glargine, which has been shown to have increased affinity for the IGF-1 receptor compared to human insulin^{4,5,6}.

- All Novo Nordisk insulin analogues on the market have been studied in many randomised, controlled trials, in observational studies and are furthermore monitored for any safety signals through rigorous post-marketing safety surveillance. Novo Nordisk has not identified any cancer signals for any of the three insulin analogues.
- Novo Nordisk has over the last 20 years discovered and developed insulin analogues to improve the treatment success rate for people with diabetes. Extensive clinical testing has provided evidence that Levemir[®], NovoRapid[®]/NovoLog[®] and NovoMix[®]/NovoLog[®] Mix 70/30 possess clinical advantages for many patients with diabetes compared to human insulin.

Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk, says: "Our science-driven approach to the discovery and development of safe, improved insulin analogues, together with the existence of comprehensive insulin safety databases, convinces us that our insulin analogues improve treatment outcomes in diabetes patients relative to human insulin."

Conference call

On 29 June at 8 am CET, corresponding to 2 am EDT, a conference call for investors will be held. Investors will be able to listen in via a link on the investor section of novonordisk.com. Presentation material for the conference call will be made available approximately one hour before on the same page.

About insulin and IGF-1 receptors

Insulin can bind to two different receptors: insulin and IGF-1 (insulin-like growth factor-1) receptors. The former mainly causes glucose lowering whereas the latter mainly induces cell proliferation. Insulin binds much stronger (more than 500-fold) to the insulin receptor than to the IGF-1 receptor and it is if this binding profile is unfavourably changed due to alterations in the insulin molecule that an insulin analogue can increase the risk of cell proliferation via the IGF-1 receptor.

Novo Nordisk is a healthcare company and a world leader in diabetes care. In addition, Novo Nordisk has a leading position within areas such as haemostasis management, growth hormone therapy and hormone replacement therapy. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to patients, the medical profession and society. With headquarters in Denmark, Novo Nordisk employs more than 27,900 employees in 81 countries, and markets its products in 179 countries. Novo Nordisk's B shares are listed on the stock exchanges in Copenhagen and London. Its ADRs are listed on the New York Stock Exchange under the symbol 'NVO'. For more information, visit novonordisk.com.

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References:

¹ www.diabetologia-journal.org/

² Baserga R, Peruzzi F, Reiss K (2003): The IGF-1 receptor in cancer biology. *Int J Cancer* 107: 873-877

³ Gammeltoft S, Hansen BF, Dideriksen L, Lindholm A, Schäffer L, Trüb T, Dayan A, Kurtzhals P (1999): Insulin aspart, a novel rapid-acting human insulin analogue. *Exp Opin Invest Drugs* 8 (9): 1431-1442

⁴ Kurtzhals P, Schäffer L, Sørensen A, Kristensen C, Jonassen I, Schmid C, Trüb T (2000): Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 49: 999-1005

⁵ Center for Drug Evaluation and Research, FDA. Application number 21-536: Pharmacology review of insulin detemir

⁶ Shukla A, Grisouard J, Ehemann V, Hermani A, Ensmann H, Mayer D (2009) Analysis of signalling pathways related to cell proliferation stimulated by insulin analogs in human mammary epithelial cell lines. *Endocrine-Related Cancer* 16: 429-441