

Association between use of human insulin and insulin analogues and risk of cancer

1. Introduction

With regard to an increased risk of cancer associated with human insulin and insulin analogues (see Table, to be referred to as “insulin preparations” in the following text), no specific precaution has been included in the package inserts so far. It was concluded at the time of the approval review that, considering their clinical dose, the insulin preparations are unlikely to affect safety in humans, although cell growth activity and development of breast tumors had been noticed in non-clinical studies.

However, a number of study reports on an increased risk of cancer in association with insulin preparations have recently been submitted to Pharmaceuticals and Medical Devices Association (PMDA).^{1,2)} On June 26, 2009, four epidemiological studies regarding an increased risk of cancer in association with insulin glargine were published in the Journal of the European Association for the Study of Diabetes (EASD)³⁻⁶⁾ and, following this, European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) announced on June 29, 2009 and July 1, 2009, respectively, that patients with diabetes taking insulin glargine are advised to continue their treatment and they should consult their doctor, while EMA and FDA began to review the association insulin glargine and the risk of cancer.^{7,8)}

In Japan, the Japan Diabetes Society announced on July 1, 2009, that patients being treated with insulin glargine are recommended to continue their treatment and consult their doctor,⁹⁾ and PMDA posted its announcement on PMDA InfoWeb on July 13, 2009.¹⁰⁾

On the basis of the above, PMDA has conducted a review of insulin preparations, including insulin glargine, with respect to their association with increased risk of cancer and assessed whether safety measures are necessary. The results of the review are summarized in this section.

2. Literature on increased risk of cancer

A review of the literature on the association between use of insulin preparations and increased risk of cancer was performed in the categories of 1) epidemiological studies, 2) non-clinical studies, and 3) measures taken by foreign regulatory agencies.

1) Epidemiological studies

As a result of the investigation of available published epidemiological studies regarding an increased risk of cancer in association with insulin preparations, it was found that there are studies that insulin glargine showed both increased risk of cancer^{2, 6, 11-20)} and no risk compared with the other insulin preparations^{6, 21-25)}. It was mentioned that insufficient adjustment for confounding factors such as family history was present as a limitation in a number of epidemiological studies.

Regarding insulin glargine, in particular, it was found that there are studies that insulin preparations showed both increased risk of cancer³⁻⁵⁾ and no risk^{3,4)} compared with the other insulin preparations.

2) Non-clinical studies

The non-clinical data submitted at the time of application for approval of insulin analogues demonstrated that cell proliferation induced by insulin analogues is of a similar magnitude to that induced by human insulin, and therefore, at the time of approval review, it was concluded that it was not necessary to include any specific precautions in the package insert.

After approval of insulin analogues, studies on the influence of insulin analogues on cancer cell proliferation have been published,^{26,27)} in which cell proliferation activity level of insulin analogues was reported to be similar to that of human insulin.

3) Measures taken by foreign regulatory agencies

Package inserts used in foreign countries do not include any information giving precaution of an increased risk of cancer.

FDA announced on July 1, 2009, that it had started reviewing data regarding an increased risk of cancer associated with insulin glargine.⁸⁾ EMEA concluded on July 23, 2009, that the currently available data does not suggest a causal relationship between insulin glargine and cancer, and that changes of the current treatment is therefore not necessary. However, the press release stated that EMEA requested the marketing authorization holder (MAH) of insulin glargine to develop a strategy for generation of further research in this area.²⁸⁾

3. Results of the review regarding necessity of safety measures

On the basis of the currently available data regarding a possible increased risk of cancer associated with insulin preparations, taking into account of the expert's discussion, PMDA has evaluated the necessity of implementing new safety measures, and has concluded that, at this time, no additional safety measures are needed for insulin preparations including insulin glargine, for reasons (1) and (2) stated below.

(1) Association between use of insulin preparations in general and risk of cancer

- 1) In the epidemiological studies regarding an increased risk of cancer in association with insulin preparations, it was found that there are studies that insulin glargine showed both increased risk of cancer and no risk compared with the other insulin preparations. Insufficient adjustment for confounding factors such as family history was present as a limitation in most of those studies. Therefore, they cannot be considered to provide sufficient evidence that confirms a causal relationship between insulin preparations and an increased risk of cancer.
- 2) The non-clinical data submitted at the time of application for approval of insulin analogues demonstrated that cell proliferation induced by insulin analogues is of a similar magnitude to that induced by human insulin. Therefore, it was concluded at the time of approval review, that it was not necessary to include any specific precaution in the package insert. Also, a review of several reports published after the approval did not lead to a change in this conclusion.
- 3) Package inserts used in foreign countries do not currently include any information giving precaution of an increased risk of cancer.

(2) Association between use of insulin glargine and risk of cancer

- 1) Regarding insulin glargine, it was found that there are studies that insulin preparations showed both increased risk of cancer and no risk compared with the other insulin preparations in epidemiological studies. Those results were found to be inconsistent
- 2) Non-clinical studies showed that cell proliferation induced by insulin glargine is of a similar magnitude to that induced by human insulin. Furthermore, when compared with cell proliferation induced by other insulin analogues, insulin glargine was not considered to be associated with an increased risk of cancer.
- 3) Regarding increased risk of cancer in association with insulin glargine, EMEA does not consider it necessary at the present time to take any action, and package inserts used in foreign countries do not include any information giving precaution of an increased risk of cancer.

4. Future safety measures

At present, given that the association between insulin preparations and cancer has not been suggested, PMDA does not consider it necessary to alert the risk of cancer. However, it will continue to closely watch out for further reports on the matter, and to consider necessary safety measures in the future.

<References>

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Table

Nonproprietary name	Brand name	MAH
Human insulin	Novolin R Injection 100 U/mL, etc. Humulin R Injection 100 U/mL, etc.	Novo Nordisk Pharma Ltd. Eli Lilly Japan K.K.
Insulin aspart	NovoRapid Injection 100 U/mL, etc.	Novo Nordisk Pharma Ltd.
Insulin glargine	Lantus Injection 100 U/mL, etc.	sanofi-aventis K.K.
Insulin glulisine	Apidra Injection 100 U/mL, etc.	sanofi-aventis K.K.
Insulin detemir	Levemir Injection Penfill, etc.	Novo Nordisk Pharma Ltd.
Insulin lispro	Humalog Injection 100 U/mL, etc.	Eli Lilly Japan K.K.