

## Position Statement of the International Society for Pediatric and Adolescent Diabetes on Glargine and Cancer Risk

On June 26, 2009, four studies with an accompanying editorial were published online in *Diabetologia*, the journal of the European Association for the Study of Diabetes (EASD). Performed in Germany, Sweden, UK and Scotland using large diabetes and cancer databases, these retrospective epidemiologic studies investigated the risk of malignancy in patients treated with insulin analogs, in particular insulin glargine (brand name Lantus®, Sanofi Aventis). As these results have been discussed extensively in the public it is likely that it will lead to a considerable insecurity of pediatric patients treated with insulin analogs.

ISPAD supports the statements of other societies such as the American Diabetes Association ADA, LWPES, FDA and European Medicines Agency EMEA that on the basis of the currently available data, a relationship between insulin glargine and cancer cannot be confirmed nor excluded, and the concerns require further in-depth evaluation.

Clearly, there was no distinct evidence of harm in type 1 diabetes or in patients taking insulin glargine in combination with other insulin analogs. Patients and parents should be made aware that the link between insulin and cancer has been suggested but not proven and only in subgroups of adults with type 2 diabetes mellitus taking insulin glargine (Lantus®) monotherapy. As the disease process in type 2 diabetes (hyperinsulinism and insulin resistance) is completely different from type 1 diabetes (insulin deficiency) these studies have no relevance for children with type 1 diabetes. Furthermore, serious concerns have been raised regarding the data analysis, so that even the conclusions regarding type 2 diabetes may be flawed. In addition, the rapid acting insulin analogs insulin lispro, insulin aspart, were not implicated with an increased cancer risk in these studies. The long-acting insulin analog detemir and the rapid-acting analog insulin glulisin were not included in any of the analyses. The authors of the four *Diabetologia* studies and the accompanying editorial caution against over-interpretation of the limited data available to date, and state that no firm conclusions can be drawn. Individual patient concerns should be addressed with their treating physicians.

ISPAD does not recommend that patients receiving insulin glargine should be switched to an alternative basal insulin. Also, with the current knowledge and the proven benefits of the drug particularly regarding the lower rate of hypoglycemia compared to human insulin, no reason for a recommendation not to start pediatric patients on glargine is warranted. Therapeutic

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alternatives may be considered in type 2 diabetic patients with preexisting cancer or an increased familial breast cancer risk. Patients and parents should be made aware that the link between insulin and cancer has been suggested but not proven, and only in adults with type 2 diabetes mellitus.

ISPAD supports further research into the long-term safety of all the insulin analogs.

This statement does not substitute the individual consultation of a physician and should not lead to therapeutic changes without prior discussion with the healthcare team.

For the Steering Committee and the Advisory Council of ISPAD

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**ISPAD President**

**Ragnar Hanas, MD, PhD**  
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**For more information, please refer to the EASD website:**  
<http://webcast.easd.org/press/glargine/glargine.htm>.

the EMEA website  
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/Lantus/40847409en.pdf>

the FDA website  
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm170089.htm>

**For information of the ISPAD membership we wish to summarize the available information to date based on statements and available information so far on the following pages.**

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## Frequently Asked Questions (FAQ's) on Malignancy and Insulin Analogs (study results are adapted from a statement of the German Diabetes Association)

### Should the insulin therapy be changed on the basis of the knowledge from the current studies?

The authors and several scientific societies agree that the current evidence does not allow a final judgment regarding the potential association of cancer development and insulin glargine. For example, the ADA has issued this statement: "Findings from these research papers are conflicting and inconclusive, and the American Diabetes Association cautions against over-reaction until more information is available". However, a careful analysis of the data is necessary. Therefore, ISPAD supports the EASD position calling for an assessment of this therapy on an individual basis. The EASD point to potential alternatives in their statement: human insulin or a combination of short- and long-acting analogs (which were not investigated in the German study, see below) did not show an increased cancer risk. Patients with type 2 diabetes that are already affected by cancer or have a familiar breast cancer risk, should discuss such alternatives with their physician. Patients without such history should not draw any premature conclusions – says the EASD.

The potential, presently unproven risks have to be balanced against the unchallenged advantages of a therapy with glargine. As referenced in the evidenced-based ISPAD Clinical Practice Recommendations these analogues have reduced day-to-day variability in absorption compared to NPH-insulin. So far the reduction in hypoglycemia and not in HbA1c is the most prominent feature for glargine. A metaanalysis of pediatric studies in the past six years of once daily insulin glargine failed to show an improved HbA1c but found a reduced rate of hypoglycemia and a greater treatment satisfaction compared to conventional basal insulins. Thus any change to intermediate acting human insulin could lead to an increased risk of hypoglycemia and an increase of fasting glucose in such individuals where the course of action of intermediate insulin overnight does not last sufficiently long. Such potential drawbacks have to be considered in any discussion of a change in the therapeutic regimen.

### Can one draw general conclusions regarding insulin analog treatment in general on the basis of those new studies on Lantus?

No. Of particular importance that these data do not allow any conclusions regarding the treatment of type 1 diabetes which has a different etiology and pathophysiology compared to type 2 diabetes. Also no conclusions should be drawn regarding the treatment with other insulin analogs from these studies (Detemir (Levemir®), Lispro (Humalog®), Aspart (Novorapid® or Novolog®) and Glulisin (Apidra®). Subgroup analysis in patients

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treated with aspart or lispro were included in the German study and did not show an increased cancer risk.

### **How was the German analysis of the AOK sick fund data by the members of the Institute for Quality and Efficiency in Health Care (IQWiG) designed (Hemkens LG et al)?**

They analysed the data of almost 300,000 patients above age 18 years with diabetes in Germany insured at the German Local Health Care Fund AOK. They had prescription data allowing conclusions of insulin and other medications and disease codes. Patients with diagnosis codes associated with malignant diseases were excluded. Other exclusion criteria were combinations of human insulin and insulin analogs or combinations of different analogs. Final analysis was performed on approximately 96,000 patients with human insulin only, approximately 4,100 patients with insulin aspart only, approximately 3,300 patients with insulin Lispro only and approximately 23,900 patients with Insulin Glargine only. Oral antidiabetic agents were allowed and were significantly different between the groups. Also, the other concomitant therapy was significantly different. Potential other risk factors such as BMI, smoking or social status were not known and could therefore not be included into the analysis. Primary endpoint was the new diagnosis of a malignant disease.

### **Which results did the German study show ?**

Both human insulin and analog insulin showed an association between insulin dose and cancer risk. This finding does not come as a surprise as insulin resistance is associated with cancer risk. However, it does not prove a causal relationship (insulin causes cancer). As the average dose of glargine was lower than human insulin, the Lantus group had even a lower unadjusted cancer rate than the human insulin group. However, if this data was adjusted for the used insulin dose and other interactions the glargine group had an elevated relative risk for cancer of 1.19 (1.09-1.29). This calculated relative risk compared to human insulin increased by dose: 1.09 (1.0-1.19) with 10IU, 1.19 (1.1-1.30) with 30 IU and 1.31 (1.20-1.42) with 50 IU. For insulin aspart and lispro no increased risk was found in these calculations.

### **Why is this study controversial ?**

The increased risk was found only after statistical adjustment for dose and only when glargine was the only prescribed insulin; such corrections may lead to false-positive results. As any combination of other insulins with glargine was excluded from the analysis, the majority of patients taking glargine were excluded from the analysis. Thus it is likely that particularly obese and insulin resistant patients would have been included in this group. It is known that both conditions lead to a significant increase in cancer risk per se. On the other hand the group with human insulin included patients taking other insulins such as

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regular insulin or rapid acting analogs as well and may have also included a significant proportion of patients with type 1 diabetes. Furthermore, the general problem of the retrospective study design is that it does not allow conclusion about a causal relationship. The cancer risk may be increased through other factors that are related to the glargine doses. One argument in favor of this hypothesis is the relatively short period of observation (1.3 years!), as it is unlikely that the analog has caused tumors in such a short period of time. The retrospective analysis also bears the danger of an allocation bias, i.e. that physicians were more likely to have prescribed the drug in more advanced disease states. In addition, one may consider the survival bias, as patients may have survived longer by treatment and thus were able to develop cancer. Finally the adjustment for well-known risk factors such as BMI (as marker of insulin resistance or family history) were lacking.

In addition, the increased cancer risk was only found after adjustment for insulin dose. The authors assume that there would be linearity between dose and cancer risk without actually providing data for linearity. Without such adjustment the data look quite different: unadjusted analysis reveals an even reduced cancer rate with glargine. Also the mortality was lower compared to the human insulin group.

Due to these difficulties in the interpretation of the data the publication of the study in *Diabetologia* was delayed by one year (three referees recommended acceptance, three others rejection) and further studies were initiated. These new analyses were unable to reproduce the described association (Currie et al.) and/or were interpreted in a way that they did not find conclusive evidence for an association between glargine and cancer (Jonasson et al., Colhoun et al.).

### **What criticisms have been raised regarding the publication strategy of the IQWiG group lead by Peter Sawicki ?**

The concerns regarding the data analysis demonstrate that an in depth discussion of the data in the scientific community may have prevented undue concern of patients and could have allowed a better knowledge of therapeutic teams for the consultations ensuing the publication of the data on the EASD website. Indeed the original submission of the German paper was more than a year ago on August 29<sup>th</sup>, 2008 before it eventually was accepted for publication in May 2009. This would have left ample time to submit the data in abstract form to scientific meetings. However, the broad scientific community became aware of these studies only on Friday evening, June 26<sup>th</sup>, 2009. Apparently certain news media had received note of these findings even ahead of the scientific community.

### **How were the other studies designed and which results did they have?**

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### **Jonassen JM et al.:**

In this Swedish study approximately 115,000 patients were analyzed that had an insulin prescription in 2005. These data were compared to the cancer register in the following two years. Three groups were formed: patients treated exclusively glargine (approximately 6,000), patients with glargine plus other insulins (approximately 20,000) and insulin treated patients without insulin glargine (approximately 89,000). Between the largest groups (no insulin glargine, other insulins + glargine) no difference in the cancer rate was found. In the group with glargine alone an increase in the risk for breast cancer by a factor of 1.99 (1.31-3.03) was found, without any effect for other cancer risks. Potential criticisms: again this is a retrospective study, the insulin doses were not taken into consideration, the groups differed in their age distribution, and it is difficult to understand why glargine alone did show an increased risk but not in combination with other insulins. The Swedish study did control for BMI and age. They did include patients with type 1 diabetes who also had an increased risk of breast cancer when using glargine only. However, the numbers were too small for statistical comparisons.

### **Colhoun et al.:**

In the Scottish study again a comparison of three cohorts was performed as in the Swedish study: Patients with insulin glargine alone (approximately 450), insulin glargine with other insulins (approximately 3,500) and only other insulins (approximately 32,000). Again, a diabetes registry was combined with a cancer registry, now with a longer observation period (4 years) compared to the Swedish study. The predominant finding was that of an even reduced cancer risk with glargine (glargine alone with glargine and other insulins combined) as human insulin, with the small group of glargine alone had a higher risk for breast cancer. As these patients were older, more overweight, more hypertensive and taking more oral agents as the controls, the authors interpret this as an allocation bias rather than an insulin glargine effect.

### **Currie et al.**

This retrospective cohort-analysis is based on data from the U.K. THIN (The Health Information Network) was founded in 2002, which collected data from 300 doctors' offices. One aspect of the study was the comparison of insulin glargine (approximately 2,300), intermediate acting human insulin (approximately 1,300), premixed insulin (approximately 2,000) and analog premixes (approximately 2,500). Important concomitant information was available (smoking, HBA1c, body weight, blood pressure) and the baseline data appears more comparable than in the other studies. A dose-dependent evaluation was not possible as was done in the Hemkens study. No differences in the cancer risk were observed between the groups.

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An important finding in this study was the protective effect of metformin on the cancer risk, alone and in combination therapy. This was apparent for colon and pancreatic carcinoma but not breast or prostate cancer.

### **Which conclusions did the authors draw?**

The patients were on 65 to 70 years old and had an overall increased cancer risk. On the basis of the German data the authors calculated that in such a subgroup of patients per year of glargine monotherapy with 10 IU per day 2 patients per 1,000 and with 50IU 8 patients of 1,000 would be affected by additional cancer. In the Swedish study, 1 woman in 1,000 was affected by breast cancer compared to the groups treated with human insulin. The authors state that their data does not allow drawing conclusions pertaining to a causal relationship but suggesting that these numbers could be used for patient counseling.

### **Are there also prospective studies?**

Scientifically more relevant than those retrospective studies are prospective studies. So far only one prospective study over 5 years has been published (Rosenstock et al. DOI 10.1007/s00125-009-1415-7). In this open-label randomized study the effect of glargine therapy compared to NPH-therapy on retinopathy was studied. This study with 500 patients in each study arm revealed no increased risk for retinopathy with glargine. The cancer data was published in a letter to the Editor. No difference was found between both treatment groups (57 vs. 62 patients, RR for glargine 0.90). The low number of probands studied over 5 years results in the fact that only a doubling in the relative risk would have been detected statistically.

### **Are there other safety data ?**

According to the manufacturer Sanofi-Aventis data of more than 70,000 patients are available with post-marketing surveillance of 24 million patient years without evidence for an increased cancer risk. An independent analysis of this data may help to clarify the issue.

### **What are the conclusions of ISPAD?**

There are serious concerns regarding the validity and the interpretation of the data. Nevertheless, taken together with cell culture data there is reason for concern and further studies and analyses will be necessary. However, ISPAD recommends in line with the recommendations of other societies that with the current knowledge and the proven benefits of the drug particularly regarding the lower rate of hypoglycemia compared to human insulin, no reason for a recommendation to discontinue glargine therapy or not to start pediatric patients on glargine is warranted. An individual evaluation of risks and benefits has to be taken together with patient and family, as with any other insulin therapy. ISPAD joins other societies and agencies in

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calling for an in-depth analysis of the available data as well as performing additional studies. We hope that the discussions instigated by those studies in the coming weeks will remain fact-based and avoid undue worry to patients and families.

This statement is put together on the basis of the currently available data and will be updated when necessary.  
July 22<sup>nd</sup>, 2009

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