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ORIGINAL REPORT

A cross-national comparison of 17 countries' insulin glargine drug labels†

Jennifer M. Polinski[1,2]*, Aaron S. Kesselheim[1,2], John D. Seeger[1,2], John G. Connolly[1], Niteesh K. Choudhry[1,2] and William H. Shrank[3]

[1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA*
[2]*Harvard Medical School, Boston, MA, USA*
[3]*CVS Caremark, Woonsocket, RI, USA*

ABSTRACT

Purpose Type 2 diabetes mellitus has reached epidemic proportions worldwide. Many patients with type 2 diabetes mellitus will require insulin, and the evidence-based use of insulin is described in the prescription drug label. Product labels in different countries may provide inconsistent information. We evaluated the variability in drug label content for one brand of basal insulin across diverse settings.

Methods We examined the drug label content pertinent to effective and safe use of insulin glargine across 17 countries: Abu Dhabi (United Arab Emirates), Argentina, Brazil, Canada, China, Germany, Israel, Italy, Japan, Mexico, Russia, Saudi Arabia, South Korea, Spain, Turkey, UK, and the USA. We compared label characteristics in settings where drug labels were governed by a local regulatory authority versus countries where labels were administered by a regional body or adopted from another locale.

Results All 17 labels cautioned that providers should consider age, illness, diet, and exercise when prescribing. Only two (12%) described care of the fasting patient. Caution was urged for patients with renal or hepatic impairment in 16 (94%) labels. Four (24%) did not describe responses to missed doses, and five (29%) failed to recommend patient counseling about the risk of hypoglycemia. Labels emerging from regional or adopted regulatory bodies reported fewer patients in efficacy studies than did labels from settings with their own drug regulatory agencies (365 ± 0 patients vs. 3560 ± 2938, $p = 0.04$).

Conclusions There is substantial variation in the content of drug labels for glargine, which may lead to international inconsistency in quality of care for diabetic patients. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—prescription drug label; insulin; hypoglycemia; drug safety; package insert; pharmacoepidemiology

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INTRODUCTION

In most countries, there is a standardized format and content for prescribing information that accompanies a prescription medication (also known as the "label", "summary of product characteristics", or "package insert").[1–3] Labels are written by the drug's manufacturer for the health professional audience and approved by the local governmental authority. They are intended to convey drug efficacy and safety data, a description of proper administration and storage, and other information essential to appropriate use.[4] The Physician's Desk Reference,[5] a compendium of these drug labels, is the most commonly used source for physicians seeking drug information.[6] In turn, health professionals are expected to share label information with patients; however, patient-provider communication of important drug information is often sub-optimal.[7] Patients frequently cite the drug label as a source of drug information. At least two-third of patients report reading and using these labels to educate themselves about the drugs they are taking.[6,8–11]

Labels are a key source of essential drug information, and often change over time as data accumulate regarding a drug's safety and effectiveness since market entry.[5,12] Many have expressed concern that labels leave out important information regarding efficacy and safety[13] while others argue that labels have become

*Correspondence to: J. M. Polinski, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120, USA. E-mail: jpolinski@partners.org
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laundry lists of hundreds of side effects, making it difficult to discern information of true importance.[12] Because the inclusion of accurate and relevant information on prescription drug labels can influence both healthcare professionals' prescription practices and patients' use of medications,[13–15] the content and variation of these labels across geographic jurisdictions is of import for global public health—the presence of text in one jurisdiction's label and its absence in another may meaningfully impact whether the public in the two jurisdictions use the drug effectively and safely.

The use of basal insulin to treat type 2 diabetes mellitus (T2DM) offers a suitable test case with which to evaluate the heterogeneity of drug labels across different regulatory authorities and geographies. The prevalence of T2DM is growing and will reach over 300 million cases by 2030.[16,17] Because of trends of diagnosis at earlier ages and the progressive nature of the disease, many patients with T2DM will eventually need treatment with insulin to achieve glycemic control targets.[18] While insulin is an effective medication, prescribers and patients alike must carefully monitor use to minimize the risks of adverse events due to overdosing or underdosing.[19] For example, a recent US study found that 41% (affecting over 10 000 patients) of unintentional hospitalizations among the elderly due to adverse drug events were for insulin overdose leading to hypoglycemia.[20] Thus, the safe and effective use of insulin is a key public health issue.

Because proper use of insulin may be mediated by the information contained in the drug label, we examined the heterogeneity of drug labels for one basal insulin, insulin glargine, across 17 countries with a high prevalence of T2DM: Argentina, Brazil, Canada, China, Germany, Israel, Italy, Japan, Mexico, Russia, Saudi Arabia, South Korea, Spain, Turkey, United Arab Emirates (Abu Dhabi), UK, and the USA. We sought to determine whether the diversity of these countries resulted in similar diversity in glargine label content and to understand the factors that might contribute to those differences.

METHODS

Setting selection

We focus on 17 of the 18 independent countries participating in the MOSAIc study, the Multinational Observational Study Assessing Insulin Use, an international observational cohort study to identify patient-, physician-, and health care environment-based factors associated with insulin intensification for patients with T2DM.[21] These 17 countries all have a high prevalence of T2DM,[22] use a variety of different drug regulatory mechanisms and organizations, include both developing and developed nations, and represent populations with heterogeneous cultural, religious, and economic concerns that may affect insulin use. The 17 countries include Argentina, Brazil, Canada, China, Germany, Israel, Italy, Japan, Mexico, Russia, Saudi Arabia, South Korea, Spain, Turkey, United Arab Emirates (Abu Dhabi), UK, and the USA; in each of these countries, insulin glargine is still a single source, patented drug. India is also participating in MOSAIc but was not included in the present study due to the extensive availability of multisource (generic) insulin glargine.

Label collection and abstraction

For each country, we obtained the glargine package insert from the local regulatory authority or from Eli Lilly. We assessed each drug label's content that was pertinent to efficacy and safety. In the USA for example, the most pertinent sections of the drug label included indications and usage, contraindications, dosage and administration, warnings and precautions, adverse reactions, use in specific populations, clinical studies, and overdose; the description and clinical pharmacology sections were not reviewed. For six countries where the package insert was not available in English (Argentina, Brazil, Japan, Mexico, South Korea, and Turkey), colleagues with proficiency in these languages translated the label text.

Three clinicians (J. D. S., N. K. C., and W. H. S.) and the lead investigator (J. M. P.) identified clinically relevant content for abstraction. From each section of the label, a trained abstractor (J. G. C.) and the lead investigator (J. M. P.) extracted information using a standardized abstraction tool, with differences resolved by discussion until consensus was achieved.

Setting classification

In an effort to explore label heterogeneity by characteristics shared by two or more countries, we created two classifications. First, we classified each country as to its method of prescription drug regulation as reported by the World Health Organization's list of Medicines Regulatory Authorities,[23] and if necessary, confirmed by personal communications with those agencies.[24] A country was defined as having *setting-specific regulation* if a local regulatory body governed the content and approval of the drug label. *Regional regulation* was defined as participation in a regional governmental union which reviewed and approved drug labels for all members, and *adopted regulation* was defined as drug label regulation borrowed from

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another country or regional union (e.g., country X waited until country Y approved the drug and then utilized country Y's label in whole). While the UK does participate in the European Union's European Medicine's Agency,[25] the UK label had marked differences as compared with other European Union countries, suggesting additional oversight by the Medicines and Healthcare Products Regulatory Agency.[26] We therefore defined the UK as having setting-specific regulation. For analysis, we grouped the countries with the two outsourced regulatory systems (regional-level and adopted regulation). We hypothesized that setting-specific regulations might be associated with more culturally relevant label content than regional or adopted regulation, for example, information on care of the fasting patient in countries where Ramadan fasting might be common. Other aspects of demographic or biological diversity, such as racial and ethnic background, socioeconomic status, or prevalence of obesity might also encourage labels' mention of country-specific considerations.

Countries were additionally classified according to their economic development status as defined by the International Monetary Fund.[27] Developed countries included the USA, the UK, Canada, Germany, Spain, Italy, and Japan. Remaining countries were categorized as developing. We hypothesized that developed countries might have lengthier, more detailed labels than developing countries due to increased capacity for legislation and/or more developed regulatory systems with more extensive requirements for drug labels.

Analysis

All data were evaluated descriptively. Differences across regulatory type and across economic development level were assessed using Fisher's exact tests and t-tests as appropriate. In China, the health care provider label was not released to the public, [20] so the package insert label that accompanies each dispensed prescription was used in its place. Labels in China, Japan, Russia, and Turkey did not report the number of patients in efficacy studies and so were not included in these analyses. The Chinese label did not report the number of patients in safety studies and so was excluded from that analysis. Analyses were completed in SAS 9.2 (Cary, NC).

RESULTS

Variation in drug label regulatory oversight

A total of 11 (65%) countries regulated their own pharmaceutical products and the content of drug labels. Italy, Spain, and Germany used a regional-level regulation process (specifically that of the European Union), and three countries (Abu Dhabi, Russia, and Saudi Arabia) adopted the labels of other countries.

Indications, warnings and precautions, and use in specific populations

All labels listed treatment of type 1 and type 2 diabetes mellitus as the indication for use. All labels cautioned that providers should consider age, illness, diet, and exercise when prescribing. For example, the Russian label noted "In the elderly [>65 years old], progressive deterioration of renal function may lead to a steady decrease in insulin requirements." Most labels mentioned weight ($N = 16$ [94%]), gender (13 [76%]), and breastfeeding (16 [94%]) as additional considerations when prescribing glargine (Table 1). The German label read, "Breastfeeding women may require adjustments in insulin dose and diet." While most labels urged caution for patients who missed meals, only two labels, those from Japan and Mexico, specifically noted that use in the fasting patient should be carefully monitored and that dosing adjustments

Table 1. Factors to be considered in insulin use, as described in the 17 labels

Item	Labels containing the item (N (%))
Weight	16 (94)
Age	17 (100)
Gender	13 (76)
Diet	17 (100)
Fasting	2 (12)
Exercise	17 (100)
Illness	17 (100)
Pregnancy	17 (100)
Breastfeeding	16 (94)
Donating red blood cells or other blood products	0 (0)
Recommendations for monitoring frequency	5 (29)
Refrigeration and/or freezing	17 (100)
Comorbid conditions	17 (100)
Renal impairment	16 (94)
Hepatic impairment	16 (94)
Hypothyroidism	5 (29)
Adrenocortical insufficiency	6 (35)
Pancreatic impairment	1 (6)
Acromegaly	1 (6)
Cushing's syndrome	1 (6)
Pheochromocytoma	1 (6)
Missed doses	13 (76)
Transition from another antidiabetic medication (oral or injected) to insulin	17 (100)
Addition of insulin to an existing antidiabetic treatment regimen	12 (71)
Method to increase insulin dose	13 (76)
How to address mild hypoglycemia	16 (94)
How to address serious hypoglycemia requiring hospitalization	16 (94)

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might be needed: the Japanese label read "Caution is needed when used for patients in a state of starvation or with unstable eating habits" (translation).

All labels described at least one comorbidity for which glargine was not recommended or for which the dose should be reduced; the most common were renal and hepatic impairment. The US label read

> *Due to its long duration of action, [glargine] is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia…a reduction in the [glargine] dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins.*

Dosing and administration

Information regarding the dosing and administration of glargine was variable across labels. While five (29%) labels included a recommended starting dose of 10 units per day, another 11 (65%) provided no starting dose recommendation. Japan's label recommended a starting dose between four and 20 units per day: "For adults, treatment should usually be initiated at 4-20 units per day injected subcutaneously, with or without concurrent treatment with other insulin products" (translation). All labels described how to transition from another antidiabetic medication to glargine: for example, the Chinese label specified

> *When initial twice-daily NPH insulin patients are changed to once-daily [glargine], basal insulin dosage should be reduced by 20–30% (compared to total dose of NPH) during the first week. When basal insulin dose is reduced, some patients may then need compensatory insulin at mealtimes. Afterwards, treatment should be individualized (translation).*

Twelve (71%) labels described how to add glargine to an existing antidiabetic medication regimen and 13 (76%) described factors for the prescriber to consider prior to increasing the glargine dose:

> *In case of inadequate glycemic control or the tendency for hypo or hyperglycemic episodes to occur, other factors such as patient's adherence to the prescribed treatment, the choice of local injection site or inadequate injection techniques, or inadequate handling of the apparatus for injection and all other relevant factors should be reviewed before considering a dose adjustment (UK label).*

Label text often recommended what to do if a patient missed a dose or took less glargine than prescribed:

> *Ask the doctor about what procedure to adopt in case of having administered a dose that is more or less than prescribed of [glargine] or if you have forgotten to administer a dose…If you have forgotten a dose or administered a much smaller dose of [glargine] than prescribed, your blood sugar level may elevate substantially. Check your blood glucose level frequently. (Brazilian label, translated).*

Four labels (24%) did not describe what to do if a dose was missed.

Dosage warnings for patients with adrenocortical insufficiency were found in 6 (35%) labels and hypothyroidism in 5 (29%) labels; for example, the South Korean label noted

> *Careful monitoring of patients is required in the following conditions because of increased susceptibility to hypoglycemia. The dose of insulin glargine may need to be adjusted: endocrine disorders, hypothyroidism, anterior pituitary or adrenal glucocorticoid insufficiency (translation).*

> *Canada's label contained these additional advisements: "[T]he presence of diseases such as acromegaly, Cushing's syndrome, hyperthyroidism and pheochromocytoma can complicate the control of diabetes mellitus."*

Adverse drug reaction categories

The total number of adverse drug reactions (ADRs) reported across countries ranged from four in Brazil to 41 in Argentina (mean 14, standard deviation ±10). Over 75% of countries reported fewer than 10 ADRs (data not shown). These most common ADRs included: allergic reactions, hypoglycemia, dysgeusia, visual impairment, retinopathy, lipohypertrophy, lipoatrophy, myalgia, injection site reactions, and edema. All labels reported hypoglycemia among the most serious ADRs; however, not all labels reported other serious ADRs (Figure 1). Two labels (12%) cited loss of consciousness as a potential ADR. Canada's label was singular in describing death, infection, seizure, and irregular heartbeat among serious ADRs. Among countries that use the black box warning mechanism on their drug labels, Canada was the only label with a black box warning for serious hypoglycemia.

Patient counseling information

Recommendations in the label as to what information prescribers should communicate to their patients were

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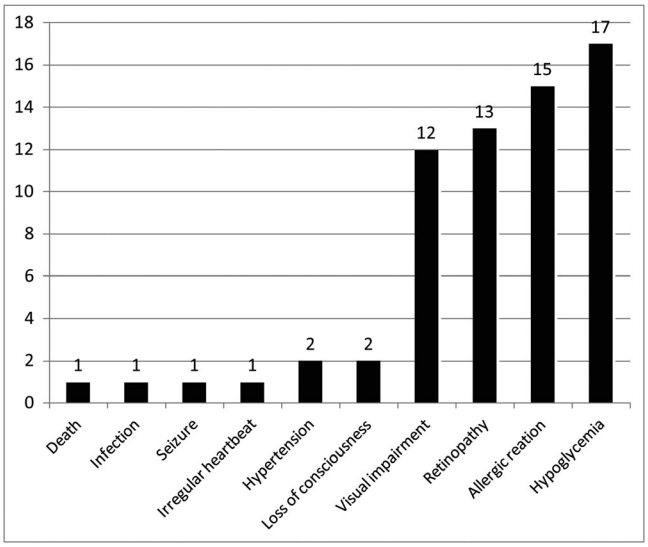

Figure 1. Most common serious adverse drug reaction categories reported in 17 international glargine drug labels

Table 2. Description of patient counseling information in 17 international insulin glargine drug labels

Patients should:	Labels containing the item (N (%))
Make changes to their regimen in consultation with their provider	15 (88)
Rotate the insulin injection site	17 (100)
Not mix or dilute this insulin	16 (94)
Not share needles or devices with others	9 (53)
Be trained in methods to monitor their glucose levels	16 (94)
Be trained in injection technique	16 (94)
Be told that side effects may include:	
Weight gain	3 (18)
Allergic reaction	12 (71)
Hypoglycemia	12 (71)

inconsistent across countries (Table 2). Labels from Brazil, Mexico, Israel, South Korea, and Japan ($N = 5$ [29%]) did not have a specific patient counseling section within the provider label. Most, but not all, labels discussed the need for patients to be trained in glucose monitoring and injection ($N = 16$ [94%]). Only three (18%) labels mentioned weight gain as a possible side effect of insulin use and 12 (71%) recommended that patients be told about possible hypoglycemia or allergic reactions.

Differences in content across countries by development status and regulation

As described in the Methods section, 13 countries reported efficacy study, and 16 countries reported safety study information. Among the countries whose labels reported information, labels from developed countries reported similar numbers of patients in efficacy and safety studies and similar numbers of ADRs as compared with those from developing countries. When compared across regulatory mechanisms, countries that had regional or adopted regulation described many fewer patients in efficacy studies than did countries that imposed their own drug regulation, mean ± standard deviation 365 ± 0 patients versus 3560 ± 2938, $p = 0.04$, (Table 3). However, countries with regional or adoption regulations reported similar numbers of patients in safety studies (3228 ± 2639 patients versus 1328 ± 149 patients, $p = 0.1043$) and reported analogous numbers of ADRs (17 ± 13 versus 10 ± 0) in comparison to countries with their own regulatory framework.

DISCUSSION

We found substantial variation across 17 countries in the content of drug labels for insulin glargine. Certain labels lacked guidance regarding missed doses, fasting considerations, and adding insulin to an existing antidiabetic medication regimen. Recommendations for patient counseling failed to mention hypoglycemia as a possible adverse effect about one-third of the time. A country's regulatory framework was associated only with the number of patients described in efficacy studies, and a country's economic status was not associated with label attributes. While the present study focused on

Table 3. Characteristics of 17 international insulin glargine drug labels, by economic development status and type of regulatory body

Economic development status	Developed	Developing	*p*
	Mean +/− standard deviation		
N patients in efficacy studies	2560 ± 3757	2136 ± 1858	0.8
N patients in safety studies	2787 ± 3094	2305 ± 1499	0.7
N reported adverse drug events	18 ± 11	11 ± 10	0.3
Regulatory body	Setting-specific regulation	Regional or adopted regulation	*p*
	Mean +/− standard deviation		
N patients in efficacy studies	3560 ± 2938	365 ± 0	0.04
N patients in safety studies	3228 ± 2639	1328 ± 149	0.10
N reported adverse drug events	17 ± 13	10 ± 0	0.2

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a single drug, our findings are consistent with a number of studies showing cross-national differences in medical product information.[28,29]

Hypoglycemia is the most common ADR associated with insulin use. In the USA alone, 41% of unintentional hospitalizations for adverse drug events among the elderly are due to hypoglycemia from insulin overdose.[20] The 17 labels we reviewed often lacked guidance about factors that might influence overdosing and underdosing such as missed doses and care of the fasting patient. Interestingly, the labels from Mexico and Japan were the only ones that specifically mentioned fasting, despite the fact that we included several countries with large numbers of citizens who fast during Ramadan, Yom Kippur, or other religious holidays. Although religions exempt members in poor health from fasting, people may choose to fast anyway.[30–32] The absence of information regarding fasting suggests a public health hazard as well as a missed opportunity to provide information of particular cultural and religious significance in those locations.

Approximately one-third of labels offered no guidance about adding glargine to an existing antidiabetic medication regimen. The current American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) guidelines recommend discontinuation of sulfonylureas and meglitinides when insulin is initiated in order to mitigate the risk of hypoglycemia,[18] yet such information was not presented in these labels. Similarly, we found five labels that failed to recommend patient counseling about the risks of hypoglycemia. Healthcare providers can and do provide patient counseling independently from guidance included in the drug label, but at least 1/3 of patients have difficulty remembering medication information conveyed during office visits, and among those patients, 42% forgot potential side effects.[33] Survey-based studies found that at least 62% of patients report reading the drug label themselves and view it as an important source of information about drugs.[9–11] Simply offering hypoglycemia counseling in the label will not fully resolve gaps in patients' awareness of medication use; however, given the incidence and seriousness of hypoglycemia among patients with T2DM and the need for patients to recognize signs and symptoms of hypoglycemia in order to mitigate its effects, the absence of this information from the label seems a missed opportunity to reduce patients' risk of adverse outcomes.

Differences across labels may reflect countries' regulatory approaches, economic status, and/or the role of the label in legal proceedings. Surprisingly, we found no differences in the number of patients in safety studies or the number of ADRs reported between countries that regulated their own drug products versus those that used adopted or regional approaches. Similarly, we did not find differences between countries classified as developed versus developing that might explain variation in label content. An alternative explanation is that manufacturers design different labels in each country in response to other facets of the pharmaceutical market or regulatory process that we did not measure. Another explanation is that label heterogeneity may reflect the timing of drug approval in each international setting, as relevant information about the drug, including its associated adverse events, accumulate over time.

Our study is limited in that the organization of label content varies across countries. If there was doubt as to the pertinence of a given section to efficacy and/or safety, that section's text was abstracted, minimizing the possibility that we left out relevant information. We did not examine the impact of drug label differences on clinical outcomes such as rates of hypoglycemia. This assessment would require individual-specific data on whether each patient was using glargine and/or other antidiabetic medications, whether he discussed the drug label with his physician and/or consulted the label himself, and what his clinical outcomes were. Obtaining such patient-specific data for all 17 countries was prohibitive due to country-specific patient privacy restrictions, cost, and in most if not all cases, lack of available information on prescriber-patient discussions about labels. These data may be forthcoming from studies such as GAPP2, the Global Attitudes of Patients and Physicians Survey, a cross-national study of patients' and physicians' use of insulin and patients' experiences with hypoglycemia and may provide important insights about the impact of variations in drug labeling on public health.[34]

In the present descriptive study, we found important omissions and substantial variation across 17 international drug labels for insulin glargine. Labels lacking information about handling missed doses, warnings for use in patients with certain comorbidities, or warnings about hypoglycemia may under-inform prescribers or patients about these important health risks. In addition, variations in the number of ADRs listed, the number of patients in safety and efficacy studies, or the recommended starting dose may translate into clinically relevant differences in how the same drug is used in two different countries. Whether such variation is appropriate and well-suited to the needs of a particular setting is unknown yet crucial to determining whether drug label information standards in particular countries warrant change.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Across 17 countries' drug labels for insulin glargine, we observed variation in the number of ADRs listed, the number of patients in safety and efficacy studies, and/or the recommended starting dose.
- Some drug labels had notable omissions about handling missed doses, warnings for use in patients with certain comorbidities, and/or warnings about hypoglycemia, the absence of which may translate into clinically relevant differences in how the same drug is used in different countries.
- Whether such variations and omissions are appropriate and well-suited to the needs of a particular setting is unknown yet crucial to determining whether drug label information standards in particular countries warrant change.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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