

## **Insulin glargine in a Brazilian State: Should the government disinvest? An assessment based on a systematic review**

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(Accepted for publication in Applied Health Economics and Health Policy)

### **ABSTRACT**

**Introduction and Objective:** The costs of the insulin analogue (Insulin glargine) have been growing appreciably in the State of Minas Gerais in Brazil, averaging 291% per year in recent years. This growth has been driven by an increasing number of successful law suits and a 536% price difference between insulin glargine and neutral protamine Hagedorn (NPH) insulin. One potential way to address this is to undertake a systematic review assessing the efficacy and safety of insulin glargine analogue compared with NPH insulin in patients with Type I diabetes. As a result, provide published data to support future recommended activities by the State of Minas Gerais. These could include maintaining it on the list of the Public Health System (SUS) provided there is a price reduction. Alternatively, provide potential arguments to defend against future law suits should the authorities decide to delist insulin glargine.

**Methods:** A systematic review of published studies researching the effectiveness of insulin glargine in patients with Type 1 diabetes between January 1970 and July 2009 in Medline (PubMed), the Latin American and Caribbean Centre on Health Sciences Information, the Cochrane Controlled Trials Databases and the National Health Service (NHS) Centre for

Reviews and Dissemination. Inclusion criteria included insulin glargine on its' own or combined with other insulin formulations. Only randomised controlled clinical trials were included. Initially, the titles of all studies were assessed by two independent reviewers before being potentially discarded, with the quality of papers assessed using a modified Jadad scale. The outcome measures included blood levels of glycated haemoglobin, episodes of hypoglycaemia, adverse effects and the reduction of microvascular and macrovascular end-organ complications of T1DM.

Results: Out of 803 studies found in the selected databases, only eight trials met the inclusion criteria. Most of the studies were of poor methodological quality or had a high risk of bias with a mean score of 2.125 on the Jadad scale. No study could be classified as double-blind, and only one study documented the increased efficacy of insulin glargine in relation to both glycaemic control and hypoglycaemic episodes. Typically, there was no significant difference between insulin glargine and NPH insulins.

Conclusions: This systematic review showed no therapeutic benefit of insulin glargine over other insulin formulations studied when analysing together glycaemic control and the frequency and severity of hypoglycaemia. We therefore recommend to the State Authority to delist insulin glargine or renegotiate a price reduction with the manufacturer. This systematic review provides support for this decision as well as documentation to combat potential law suits if there cannot be satisfactory discussions.

### **Key points for decision makers**

- The costs of insulin glargine have been growing appreciably in the State of Minas Gerais in Brazil in recent years. This has been driven by an increasing number of successful law suits and substantial price differential between long-acting insulin analogues and other insulin formulations
- A thorough systematic review would provide a rationale whether to maintain insulin glargine on the list of the Public Health System (SUS) or delist it. In addition, provide potential arguments to defend against future law suits if pertinent
- The review showed no clinical benefit with insulin glargine over other insulin formulations, confirming the findings from other reviews
- This provides a basis for the State Government to seek either to delist insulin glargine or negotiate a price reduction similar to other countries

## INTRODUCTION

There is increasing scrutiny on pharmaceutical expenditure among countries, driven by expenditure rising by more than 50% in real terms between 2000 and 2009 among OECD countries [1-6]. This has been driven by well known factors including ageing populations, rising patient expectations and the continued launch of new premium priced drugs. As a result, there will be continued growth in pharmaceutical expenditure unless there are further reforms to address this. Ongoing initiatives among countries to moderate growth rates in pharmaceutical expenditure include processes to robustly assess the value of new drugs against existing standards and link this to reimbursed prices, encourage the prescribing of low cost alternatives when care is not compromised, and disinvest in products that are seen to no longer provide value [1-4, 6, 7]. An example of the latter is Sweden, which re-assessed the value of nearly 2,000 pharmaceuticals across a number of disease areas. These included drugs to treat migraine, excessive stomach acid, respiratory diseases, hypertension, depression, and hyperlipidaemia [3, 5, 8-11]. Following the review of respiratory diseases, cough medicines were delisted as the reimbursement agency (TLV) believed it was unreasonable to reimburse these medicines with only limited efficacy and for short-term conditions with only relatively minor discomfort. Four asthma treatments were delisted from October 2007 including theophyllines for maintenance treatment as they were considered not cost-effective against newer treatments [3, 5]. Prescribing restrictions have also been introduced for some patented drugs in Sweden [8-11]. These included angiotensin receptor blockers versus generic angiotensin converting enzyme inhibitors (ACEIs), patented statins versus generic statins and duloxetine [8-11]. Duloxetine was restricted to patients suffering from depression or general anxiety disorders who had been prescribed at least two other antidepressants and not reached their treatment goals [9, 11]. The French reimbursement agency has also evaluated over 4000 products. This is because products of no real therapeutic value cost the French health service over €450mn/ year before the start of the review [6]. The first wave of the reviews resulted in 72 products being removed from the reimbursement list. 282 products were removed in 2006, with more products delisted in recent years [6].

Recent reforms in Germany resulted in the delisting of atorvastatin from the reimbursement list as there was no outcome data showing superiority over generic simvastatin but a

considerably higher price [12]. IQWiG also recommended the delisting of long-acting insulin analogues as there was no outcome data demonstrating superiority over neutral protamine Hagedorn (NPH) insulins to justify appreciably higher prices in both Type I and II diabetes [13-16]. This led to price reductions of long-acting insulins soon after the initial activities to help maintain reimbursement for these drugs, which have persisted [17]. The findings are similar to those from the Cochrane Review of long-acting insulins, which also found long-acting insulins only have a minor clinical benefit, if at all, versus NPH insulins in patients with Type I or II diabetes [18, 19]. NICE in the UK in 2002 recommended NPH insulins as first line treatment in patients with Type II diabetes, with long-acting insulins only recommended in specific circumstances, with glargine a potential option for patients with Type I diabetes (14, 20). The specific circumstances were (20):

- Those who require assistance from a carer or healthcare professional to administer their insulin injections.
- Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
- Those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

Similarly, the Pharmaceutical Management Agency (PHARMAC) in New Zealand only approved long acting insulins for reimbursement as second line therapy [21]. This includes patients who are allergic to conventional insulins or have failed to control their diabetes with conventional insulins [21]. In Canada, the Canadian Agency for Drugs and Technologies in Health similarly only recommended long acting insulins in patients experiencing significant hypoglycaemia with human insulins [14]. This is perhaps not surprising with a number of published studies showing at best only modest health gain with the long-acting insulins [14, 19, 22, 23].

The State of Minas Gerais in Brazil has also introduced a number of measures to enhance the quality and efficiency of future prescribing. This includes the instigation of the Commission of Pharmaceuticals and Therapeutics (Comissão de Farmácia e Terapêutica – CFT) [24]. The Commission has a mandate to recommend the inclusion and exclusion of drugs funded by the State and distributed by the state branch of the public healthcare system (Sistema Único de Saúde - SUS/MG) [24]. The reviews are based on available scientific evidence of relative

efficacy, safety and cost-effectiveness versus current standards [24], mirroring activities in a number of European countries [3, 4, 6, 14, 25-27]. Consequently, providing a scientific basis for potential future activities and deliberations by the State authorities. This is because in Brazil the government subsidises the list of medicines to be provided to the population. When doctors do not prescribe certain drugs as they are not included in the standard list of publically available drugs, some patients subsequently sue the state to try and obtain them. This is because under Brazilian law, there is a constitutional principle of universality and comprehensiveness [28]. However, this system can be abused as illustrated by 2,412 lawsuits between October 1999 and 2009 [28], particular via the private sector. As a result, helping to serve the interest of pharmaceutical companies rather than health authorities with their fixed budgets [28]. The belief is that thorough systematic reviews will provide robust arguments to successfully combat future lawsuits.

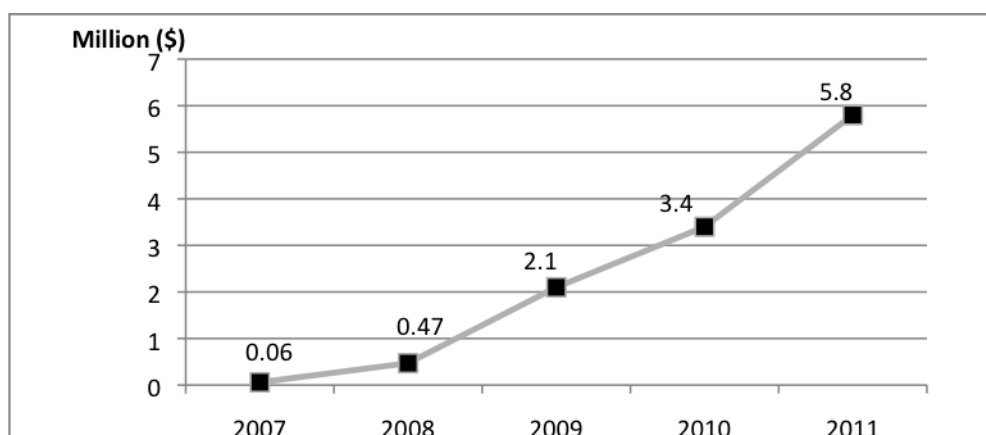
Insulin analogues were originally developed to improve the safety, efficacy and comfort of treating patients with diabetes mellitus. Such drugs have a chemical structure analogous to that of insulin and are classified as long-acting (glargine and detemir) or fast-acting (lysine-proline (lispro), glulisine and aspart).

Insulin glargine was the first insulin analogue developed. Its use in humans was approved by the European Medicines Agency in 2000, and it was introduced into clinical practice in the early years of the last decade. In Brazil, this drug was registered by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - ANVISA) in 2003, when it also began to be marketed. The drug was marketed as an improved reduction of hypoglycaemic episodes and increased comfort for patients despite limited confirmatory evidence [29], leading to a rapid uptake.

Initially, insulin glargine was not included in the medicines list of the State of Minas Gerais. However, an increasing number of lawsuits compelled the State government to include insulin glargine in 2005 in the State of Minas Gerais' List of Medicines for patients with type 1 diabetes. This though did not stop the lawsuits for patients outside the current protocol, e.g. patients with type 2 diabetes, in view of the price differential between NPH insulins and glargine insulins.

Between 2005 and 2006, insulin glargine was responsible for the third highest number of lawsuits filed against the State Health Secretary (Secretaria de Estado de Saúde - SES/MG) [30]. Overall, the number of administrative requests has grown since insulin glargine was included in the State List of Medicines, corresponding to 2,632\* people. At the same time, the expenses of Minas Gerais State Treasury with insulin glargine grew an average of 291% per year, reaching almost US\$ 6 million in 2011\*\* (Figure 1). In Brazil, the cost of treating with insulin glargine is 536% that of treatment with NPH insulin [31].

Figure 1 Expenditure on insulin glargine by Minas Gerais State, Brazil (2007-2011) in US\$



NB. There is no adjustment for inflation

In addition in 2009, CFT/SUS/MG was informed of the results of studies indicating a higher risk of malignancy in diabetic patients treated with insulin analogues [32, 33]. This, together with the concerns with the value of insulin glargine versus NPH insulins, motivated SES/MG to request to the Collaborating Centre for Pharmacoeconomic and Epidemiologic Studies of the Federal University of Minas Gerais, a partner of SES/MG in technical-scientific studies, to perform a systematic review assessing the efficacy and safety of the insulin analogue glargine in patients with type 1 diabetes (T1DM).

Consequently the objective of this study is to assess the efficacy and safety of insulin glargine compared with NPH insulin in patients with Type I diabetes based on a full systematic review of currently available evidence. This builds on previous reviews [16,18,20,22,23,34]. Subsequently, use the findings to evaluate whether to maintain insulin glargine on the list of

\*Data from the Integrated System of Pharmaceutical Assistance Management of the State Health Secretary (SES/MG) in December 2011.

\*\*Data from the Direction of High-Cost Medicines (SES/MG) in February 2012. USD 1 = BRL 1,72

the Public Health System (SUS) in the Minas Gerais State in Brazil. Alternatively, provide published data to support future recommended activities by the State of Minas Gerais. This could include suggesting that the State subsequently negotiates price reductions with the manufacturer. In addition, provide potential arguments to defend against future law suits when these occur in the absence of successful negotiations.

## **METHODS**

A systematic review was performed using the software Reference Manager to identify potentially relevant studies published between January 1970 and July 2009 in Medline (PubMed), the Latin American and Caribbean Centre on Health Sciences Information (Literatura Latino-Americana e do Caribe em Ciências da Saúde - LILACS), the Cochrane Controlled Trials Databases and the National Health Service (NHS) Centre for Reviews and Dissemination. The studies selected dealt with the efficacy/effectiveness of insulin glargine in the treatment of patients with T1DM and included a survival analysis, the definition of a response and adverse effects.

The following keywords in Portuguese, English and Spanish were used in the search: type 1 diabetes mellitus, glargine insulin, NPH insulin, regular insulin, animal NPH insulin, recombinant NPH insulin, animal regular insulin, recombinant regular insulin, humans, efficacy, effectiveness and cost-effectiveness.

An illustration of the search strategy for Pub Med is included in the Appendix (Appendix 1).

The following analysis criteria were established regarding the inclusion of studies in the review:

1. Intervention: monotherapy with insulin glargine or combined regimens with other insulin formulations
2. Type of study: randomised controlled clinical trials including comparisons between drugs used in the treatment of patients with T1DM, other insulins or best supportive care (systematic reviews of clinical trials identified during the search were also used in the comparison and discussion of results).

The exclusion criteria included the following:

- studies published in languages other than English, Portuguese and Spanish;
- studies not performed in humans
- those unrelated to T1DM
- studies lacking at least one of the outcome measures of efficacy and/or safety.

Initially, to verify whether they complied with the inclusion criteria, the titles of all the studies located were assessed. Next, two independent reviewers (AS and RN) also assessed the abstracts. A third reviewer (LD) subsequently analysed studies where there was no inter-reviewer agreement regarding potential inclusion.

The outcome measures considered included the following: blood levels of glycated haemoglobin, episodes of hypoglycaemia, adverse effects and the reduction of microvascular and macrovascular end-organ complications of T1DM.

A modified Jadad scale was used to assess the methodological quality of the randomised controlled clinical trials [35]. The assessment of the quality of the studies was also performed by two independent reviewers (AS and RN), with input from a third reviewer (LD) in cases of disagreement between the two reviewers.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (Ruling nº ETIC 0588.0.203.000-09).

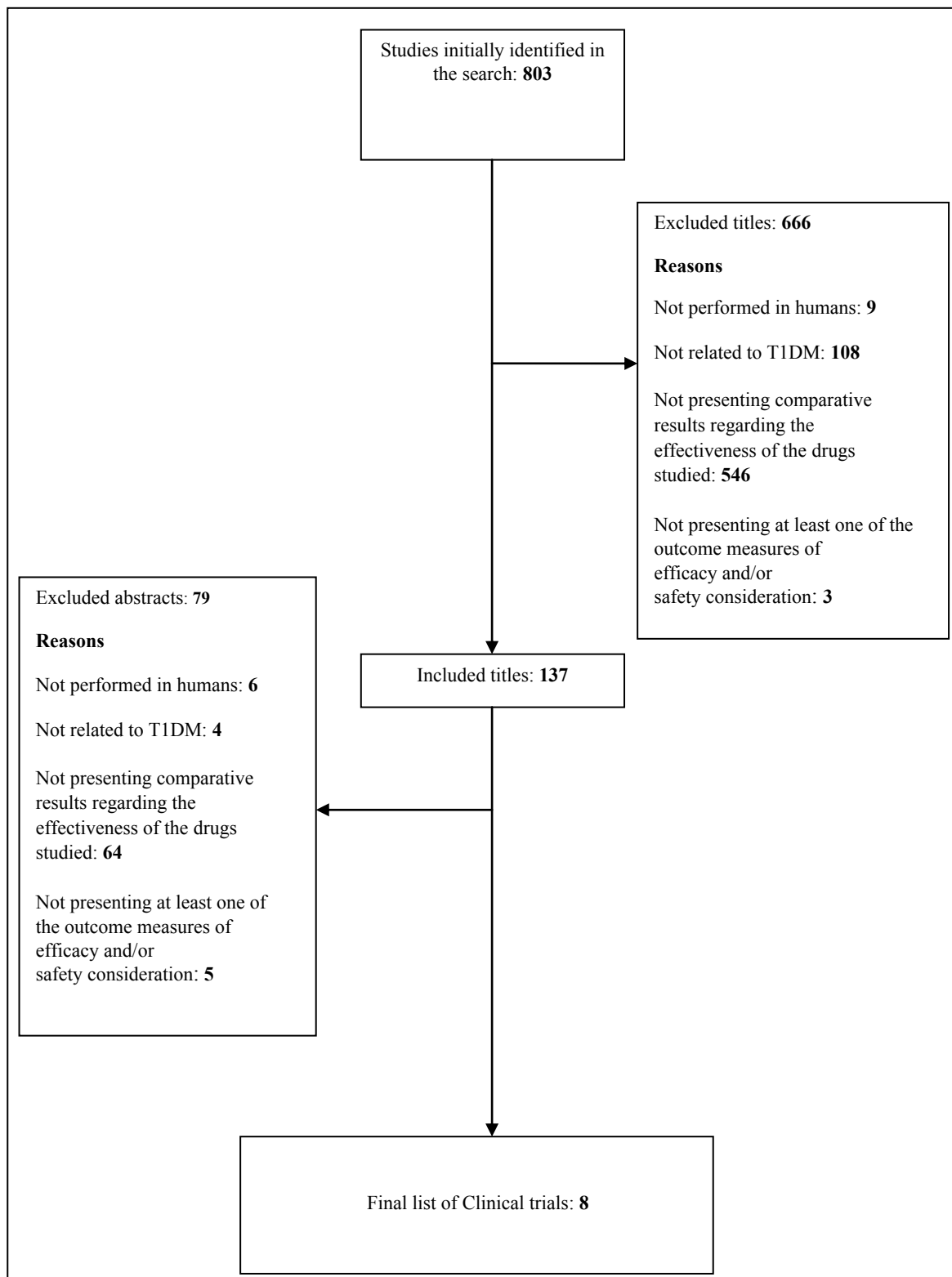
## **RESULTS**

### **Search Strategy**

The initial search strategy identified 803 titles and abstracts (Figure 2). Of these 803 studies, 666 were excluded based on their titles. These included nine studies that had not been performed in humans, 108 were not related to T1DM, 546 did not describe comparative results of the effectiveness of the investigated drugs and three did not report on at least one of the considered outcome measures of efficacy/effectiveness (blood level of glycated haemoglobin, measurements of glycaemia, episodes of hypoglycaemia, reduction of microvascular and macrovascular events, adverse effects, survival analysis). The abstracts of the remaining 137 studies were subsequently analysed. Of these, six, four, 64 and five (for a total of 79), respectively, were excluded for the same reasons mentioned above (Figure 2).



Figure 2 - Schematic presentation of the articles included and excluded in the systematic review



A total of 58 studies remained for complete review. 50 of which were classified as studies on effectiveness based on observational data; consequently, these were excluded under our inclusion criteria. As a result, only eight papers using formal clinical trials were selected for analysis. One of these could not be retrieved; consequently was excluded. However, one additional study was subsequently found and selected following a manual search, making a total of eight studies for the systematic review (Table 1).

The eight clinical trials scored an average of 2.125 points on the methodological assessment scale. According to Table 1, no study had score of 5 or 6, which represents high quality/low risk of bias. Three studies had scores of 3 or 4, which indicate appropriate quality/moderate risk of bias and five studies had a score of 0 to 2, denoting poor quality/high risk of bias. According to the Jadad criteria, the main limitations identified were: data collectors or evaluators were not blinded (eight studies); inappropriate randomisation method (five studies); lack of intention-to-treat (ITT) analysis (three studies with a further one where a full ITT analysis was not performed) and failure to describe the excluded participants or dropouts (one study) (Table 1).

Table 1 Clinical trial classification based on the modified Jadad scale

Article	Randomisation	Appropriate Randomisation	Inappropriate Randomisation	Blinding	Appropriate Blinding	Dropout/Withdrawal	Intention to Treat Analysis	Score
Rosenstock <i>et al.</i> , 2000 [37]	1	0	-1	0	0	1	1	2
Raskin <i>et al.</i> , 2000 [40]	1	1	0	0	0	1	1	4
Pieber <i>et al.</i> , 2000 [38]	1	0	-1	0	0	0	0	0
Schober <i>et al.</i> , 2002 [42]	1	0	-1	0	0	1	0*	1
Doyle <i>et al.</i> , 2004 [39]	1	1	0	0	0	1	1	4
Chatterjee <i>et al.</i> , 2007 [41]	1	1	0	0	0	1	0	3
Chase <i>et al.</i> , 2008 [43]	1	0	-1	0	0	1	1	2
White <i>et al.</i> , 2009 [36]	1	0	-1	0	0	1	0	1

\*A full ITT analysis was not performed; hence the downgrade from '1' to '0'

All of the eight clinical trial studies were open-label and investigated the use of the insulin glargine administered once per day. The lack of blinding was justified by the authors by the different physical appearances of different insulin formulations. In the study by White *et al.* (2009) [36], the assessment of the results was blinded, and in the studies by Rosenstock *et al.*

(2000) [37] and Pieber et al. (2000) [38], which compared two different concentrations of insulin glargine to another insulin formulation, the comparison between the different concentrations of insulin glargine was blinded. All of the studies were described as randomised; three among them, namely, Doyle et al. (2004) [39], Raskin et al. (2000) [40] and Chatterjee et al. (2007) [41], mentioned the method used for randomisation. An ITT analysis was described in five studies; however, in one of them, Schober et al. (2002) [42], the analysis was not performed on the full ITT population and thus was rated as inappropriate. As a result, this study was downgraded on its modified Jadad score (Table 1).

### **Characteristics of the eight clinical trials**

Seven studies compared the efficacy of insulin glargine to NPH insulin, and the study by Doyle et al. (2004) compared the efficacy of insulin glargine to the continuous subcutaneous insulin infusion (CSII) of the analogue aspart [39]. None of the selected clinical trials compared the two long action analogues available, namely, insulin glargine and detemir. The median number of participants included was 168 (range 32-619), and the duration of follow-up varied between one month (Rosenstock et al., 2000 and Pieber et al., 2000) [37, 38] and two years (Chatterjee et al., 2007) [41] with a median of four months (Table 2).

With respect to the loss of participants during the study, Pieber et al. (2000) did not mention how many patients completed the study [38]. In the study by White et al. (2009), 23.4% of participants were lost [36], and in the remainder of studies, the loss was less than 12% (Table 2).

**Table 2 Characteristics of the selected clinical trials**

Trial	Age group	Sex (female) (n, %)	Ethnic group (n, %)	Intervention	Trial aim	Participants (n)	Follow-up period (months)	Participants included trial n (%)	Sponsor	Jadad score
Rosenstock et al (2000) United States of America [37]	18-70	Insulin glargine 30 40 Insulin glargine 80 42 NPH Insulin 41 Total 123 (48%)	white 93,8%	Insulin Glargine + regular Insulin NPH + regular	To assess two formulations of insulin glargine in safety and efficacy in treating patients with T1DM.	257	1	256 (99,6)	Sanofi-aventis	2
Raskin <i>et al</i> (2000) Canada [40]	18-80	306 (49,4%)	white 600 black 16 hispanic 9 others 3	Insulin Glargine + lispro NPH Insulin + lispro	To assess insulin glargine efficacy and safety as a basal component in T1DM.	619	4	588 (94,9)	Sanofi-aventis	4
Pieber <i>et al</i> <sup>7</sup> (2000) France [38]	18-70	130 (39%)	-	HOE 901 + regular NPH + regular	To compare the efficacy of HOE 901 with NPH in T1DM.	333	1	-	Sanofi-aventis	0
Schober <i>et al</i> (2002) Austria [42]	5-16	Insulin glargine 77 (44,3%) NPH Insulin 91 (52%) total 168 (48,1%)	-	Insulin glargine + regular NPH Insulin + regular	To compare efficacy and safety of insulin glargine with NPH T1DM children and adolescent.	361	6	349 (96,7)	Sanofi-aventis	1
Doyle et al (2004) United States of America [39]	8-21	18 (56,2%)	white 24 hispanic 5 black 3	Insulin Glargine + aspart aspart	To compare the efficacy of CSH to MDI with insulin glargine in lowering HbA <sub>1c</sub> levels in children and adolescents with type 1 diabetes.	32	4	31 (96,8)	Sanofi-aventis Novo Nordisk	4
Chatterjee <i>et al</i> (2007) England [41]	18-75	27 (45%)	european 58 south asian 2	Insulin glargine + aspart NPH + aspart	To compare the efficacy of insulin glargine and aspart with NPH insulin and aspart in a basal bolus regimen in type 1 diabetes.	60	2 4	53 (88,3)	Sanofi-aventis Novo Nordisk	3

Table 2 Characteristics of the selected clinical trials

Trial	Age group	Sex (female) (n, %)	Ethnic group (n, %)	Intervention	Trial aim	Participants (n)	Follow-up period (months)	Participants included trial n (%)	Sponsor	Jadad score
Chase <i>et al</i> (2008) United States of America [43]	9-17	Insulin glargine 45 (53,6%) NPH/lente 44 (52,4%) Total 52,9%	<b>white</b> insulin glargine 71 (84,5%) NPH/lente 68 (81%) <b>black</b> insulin glargine 0 (0%) NPH/lente 7 (8,3%) <b>asian</b> insulin glargine 2 (2,4%) NPH/lente 2 (2,4%) <b>hispanic</b> insulin glargine 7 (8,3%) NPH/lente 4 (4,8%) <b>multiracial</b> insulin glargine 2 (2,4%) NPH/lente 1 (1,2%) <b>other</b> insulin glargine 2 (2,4%) NPH/lente 2 (2,4%)	Insulin glargine + lispro NPH/lente + lispro	To compare efficacy and safety of insulin glargine with NPH T1DM children and adolescent.	175	6	157 (89,7)	Sanofi-aventis	2
White <i>et al</i> (2009) United States of America [36]	9-17	42 (46,6%)	white 81 asian 2 hispanic 5 multiethnic 1 other 1	Insulin glargine +lispro NPH/lente + lispro	To compare efficacy and safety of insulin glargine with NPH/lente T1DM children and adolescent used as a basal component of a regime of multiple daily injections.	90	6	69 (76,6)	Sanofi-aventis	1

T1DM: Type 1 diabetes mellitus; NPH: Neutral Protamine Hagedorn; HbA1c: Glycated hemoglobin; CSII: Continuous Subcutaneous Insulin Infusion; MDI: Multiple Daily Injection

## **Characteristics of participants and interventions in the eight clinical trials**

The minimum age of included participants was five years, and the maximum age was 80 years. Of the 1,591 investigated participants, 56.76% were female, and 43.24% were male. Pieber et al. (2000) [38] and Schober et al. (2002) [42] did not distinguish between different ethnic groups; in the remainder of studies, most participants were Caucasian (Table 2).

The selected studies compared insulin glargine prescribed once per day, NPH insulin administered once or twice daily as a basal treatment and the ultrafast-acting analogues lispro and aspart given in multiple injections or subcutaneous infusion as prandial components. Pieber et al. (2000) [38] and Schober et al. (2002) [42] used human regular insulin as a prandial component (Table 2).

The following reasons were given for censoring in the studies: lost to follow-up, hypoglycaemia, adverse reaction to aspart, dehydration, pancreatic cancer (unrelated to treatment), lack of a baseline assessment of glycated haemoglobin A1c (HbA1c), adverse events, problems related to the monitoring mechanisms, automatic glycaemia (continuous glucose monitoring system, CGMS) and withdrawal of consent.

Associated comorbidities were investigated but were not discussed in the selected studies.

## **Outcome measures**

The efficacy of analogous glargine was assessed in all of the eight clinical studies (Table 3). White et al. (2009) did not find any statistically significant difference between insulin glargine and NPH insulin in terms of glycaemia measured by means of continuous automatic monitoring [36]. Fasting glycaemia was significantly improved with insulin glargine in Rosenstock et al. (2000): 81 mmol/L with insulin glargine (30µg/ml zinc), 86 mmol/L with insulin glargine (80µg/ml zinc) and 87 mmol/L with NPH ( $p<0.001$ ) [37]; and in Schober et al. (2002): a 1.29 mmol/L reduction in the insulin glargine group versus 0.68 in the NPH group ( $p=0.02$ ) [42]. Raskin et al. (2000) also documented the advantages of using insulin glargine over NPH in terms of the plasma and blood levels of fasting glucose, as assessed at baseline, at the time of any outcomes and every week [40]. However, the frequency of nocturnal hypoglycaemia was lower in users of NPH insulin than with glargine ( $p=0.06$ ).

Table 3 Advantages in the reduction of Glycosylated Haemoglobin (HbA1c) and episodes of hypoglycaemia

Estudo	Statistically significant advantage in the reduction of episodes of hypoglycaemia	Statistically significant advantage in the reduction of HbA1c
Rosenstock <i>et al.</i> , 2000 [37]	NPH	*
Raskin <i>et al.</i> , 2000 [40]	NS	NS
Pieber <i>et al.</i> , 2000 [38]	Insulin glargine	Insulin glargine
Schober <i>et al.</i> , 2002 [42]	**	NS
Doyle <i>et al.</i> , 2004 [39]	**	Aspart (continuous infusion)
Chatterjee <i>et al.</i> , 2007 [41]	NS	Insulin glargine
Chase <i>et al.</i> , 2008 [43]	Insulin glargine	NS
White <i>et al.</i> , 2009 [36]	NS	NS

\* Not assessed in the study; \*\* No p value documented; NS: No statistically significant NB. White et al did find a statistically significant advantage for insulin glargine for glucose levels but this did not translate into a statistically significant reduction in hypoglycaemia

Pieber et al. (2000) found a significant difference ( $p=0.030$ ) in the overall comparison of HbA1c values in the patients using insulin glargine (30 $\mu$ g/ml zinc and 80 $\mu$ g/ml zinc), with 7.71% and 7.77%, respectively, compared to 7.88% with NPH [38]. Chatterjee et al (2007) documented a HbA1c outcome value of 8.07% in users of insulin glargine and 8.26% in users of NPH ( $p=0.04$ ) [41]. With regard to the fasting plasma glucose level, the average values were 8.42 mmol/L in insulin glargine users and 11.42 mmol/L in NPH insulin users ( $p=0.01$ ).

Only one 16-week study (Doyle et al., 2004) directly compared insulin glargine and aspart [39]. The average HbA1c levels were  $8.2 \pm 1.1\%$  in the glargine group and  $8.1 \pm 1.2\%$  in the aspart CSII group ( $p<0.05$ ). The number of patients who attained HbA1c levels  $\leq 7\%$  in the 16 weeks were two (12.5%) and eight (50%) ( $p<0.05$ ), respectively.

The literature mentions a reduction in the episodes of hypoglycaemia as a possible advantage of insulin glargine. When White et al. (2009) analysed this, they found a significant difference in the adjusted average glucose levels in the insulin glargine group at  $<50$  mg/dL ( $<2.78$  mmol/L;  $p=0.0198$ ) and  $<40$  mg/dL ( $<2.22$  mmol/L;  $p=0.0130$ ) compared to the NPH/slow-acting insulin group ( $p=0.0298$ ) [36]. However this did not translate into a statistically significant reduction in the incidence of hypoglycaemia. Pieber et al (2000) though showed insulin glargine significantly reduced the incidence of hypoglycaemia when compared to NPH insulin [38]. Chase et al also proved the superiority of insulin glargine

when they assessed the incidence of hypoglycaemia between 50 mg/dL and 70 mg/dL [43]. However, Rosenstock et al. (2000) observed a significant difference favouring NPH insulin despite insulin glargine improving fasting glycaemia [37]. All the patients in the HOE 901 glargine (80µg/ml zinc) group, 97.5% of patients in the HOE 901 (30µg/ml zinc) group and 93.2% of those in the NPH group experienced at least one episode of hypoglycaemia (p=0.030). The remainder of studies did not report any statistically significant results.

In the study by Doyle et al. (2004) [39], four patients in the glargine group experienced one episode of severe hypoglycaemia, and one patient in the continuous subcutaneous aspart infusion group developed nocturnal hypoglycaemia. However, these findings were not statistically significant.

In the study by White et al. (2009), 17.6% of patients using insulin glargine and 8.9% of those using NPH/slow-acting insulin required treatment for severe adverse events [36]. In this same study, the average time to hypoglycaemia in week 24 was statistically shorter in the insulin glargine group. In the study by Chase et al. (2008), 15 (17.6%) patients using insulin glargine and 8 (8.9%) patients in the NPH/slow-acting insulin group reported adverse reactions; however, this difference did not reach statistical significance [43]. In terms of the incidence of severe adverse events, the frequency was higher in the insulin glargine group (p<0.05) in this study.

Injection site reactions were described by four studies. Rosenstock et al. (2000) [37] and Pieber et al. (2000) [38] did not specify which group. In Raskin et al [40], pain was more common with insulin glargine (6.1%) than NPH insulin (0.35); however, haemorrhage was more common with NPH insulin at 4.2% vs. 3.2% with insulin glargine. In Schober et al. (2002) [42], injection site reactions occurred in 9.2% of patients on insulin glargine and 8.6% of patients with NPH insulin. Ketoacidosis occurred in one patient using insulin glargine in the study by Doyle et al. (2004) [39], as well as in one patient in the insulin glargine group (0.6%) and four patients (2.9%) in the NPH insulin group in the study by Schober et al. (2002) [42].

The body mass index (BMI) at baseline of the participants of all investigated studies varied between 18.8 and 25.7 and did not exhibit any significant alteration in the studies that assessed this variable during follow-up, namely, Chase et al. (2008) [43], Doyle et al. (2004) [39] and Chatterjee et al. (2007) [41].



The following diabetes complications were investigated but were not addressed by any of the analysed studies: neuropathy, nephropathy, retinopathy, heart disease, effect on the brain vessels, neoplasias and hospitalisations. Consequently, no comment could be made in our systematic review.

## DISCUSSION

This systematic review analysed the glycaemic control, as well as the frequency and severity of episodes of hypoglycaemia, that were associated with the treatment of patients with Type 1 diabetes (T1DM) with either insulin glargine or NPH insulins. Although the analysis of isolated results indicated clinical benefits from insulin glargine in patients with T1DM in terms of a reduction of fasting glycaemia, insulin glargine did not show any advantages when this parameter was analysed together with a reduction of the frequency of episodes of hypoglycaemia with the control of glycaemia assessed by means of glycated haemoglobin apart from one study (Table 3). These results are consistent with the findings from the systematic review performed by the Institute of Quality and Efficiency in Health Care (IQWiG) in Germany [13, 16, 19], the review by the Cochrane collaboration as well as other recent reviews [14, 18-21]. These various reviews have resulted in a number of health authorities across continents either delisting long-acting insulins or relegating them to second line use [13-16, 19-21, 44, 45]. For instance in Scotland, the authorities recommend that insulin glargine should only be used in patients with Type I diabetes who are ‘at risk of or experiencing unacceptable frequency and/ or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with established insulins [44]. Demand side measures routinely used in Scotland to enhance adherence to this guidance include academic detailing, monitoring of physician prescribing and financial incentives [1, 2, 46].

In the studies by Pieber et al. (2000) [38] and Chatterjee et al. (2007) [41], insulin glargine significantly reduced glycated haemoglobin levels compared to NPH insulin. However, due to the number of episodes of nocturnal hypoglycaemia, only the first study demonstrated an advantage in the use of insulin glargine (Table 3).

Frequent episodes of nocturnal hypoglycaemia are also mentioned as an argument to justify the preferential use of analogues compared to other insulin formulations. However, among the studies that analysed this variable, only three reported statistically significant results (Table 3). Raskin et al. (2000) obtained results favourable to NPH ( $p=0.06$ ) but this was not

statistically significant [40]. Pieber et al. (2000) obtained results favourable to glargine and Chase et al (2008) proved the superiority of insulin glargine when they assessed the incidence of hypoglycaemia between 50 mg/dL and 70 mg/dL [38,43].

Doyle et al. (2004) reported improved results using continuous aspart infusion compared to glargine in the reduction of HbA1c on the 16th week of treatment [39]. However, this study only included 32 patients (Table 2).

Singh et al. (2009) performed a meta-analysis which focused on the efficacy and safety of insulin analogues in the treatment of patients with type 1, 2 and gestational diabetes [22]. These researchers concluded that the fast- and slow-acting analogues exhibited little additional benefit over conventional insulin formulations in terms of the control of glycaemia or the reduction of episodes of hypoglycaemia. These authors further observed that higher quality studies with longer durations of follow-up are needed to establish whether the insulin analogues are able to reduce the risk of chronic complications of diabetes mellitus. Based on this study, the World Health Organisation requested an updated review to be assessed at the 18th Expert Committee on the Selection and Use of Essential Medicines. This review concluded that the differences between long-acting insulin analogues and human insulin formulations are notably small. There was no clear clinical advantage from the use of long-acting insulin analogues compared to human insulin, and the advantages found were inconsistent in terms of their statistical and clinical significance. In addition, the long-acting insulin analogues did not prove to be consistently cost-effective, and there is uncertainty as to their association with an increased risk for cancer. This review further emphasised the high risk of bias of the studies assessing long-acting insulin analogues, due to their low quality and the fact that many of the researchers in the studies had links to the pharmaceutical industry (2011) [47]. Consequently, endorsing the findings in our systematic review.

Several other meta-analyses have reached similar conclusions [18-20,23]. This supports the recent recommendation by the Brazilian Network for Health Technology Assessment stating that resources ought to be employed in programmes seeking to maximise the treatments available in the public healthcare network, as the current evidence does not support the superiority of long-acting insulin analogues [31].

A further issue concerning patients on insulin therapy is weight gain, which is a frequent finding in these cases. The present review was not able to reach any robust conclusions concerning the alterations of the BMI based on the selected studies.

Several studies discussed the mitogenic potential of insulin analogues. Glargine exhibits a 6.5-fold greater affinity for the insulin-like growth factor (IGF-1) receptor compared to human insulin and an eight-fold greater potential to stimulate the synthesis of DNA by human osteosarcoma cells [48]. Hemkens et al. (2009) found a higher incidence of cancer than expected in patients using glargine compared to human insulin [32]. A study performed in Sweden in 2009 found a greater incidence of breast cancer in women using insulin glargine in monotherapy compared to other insulin formulations, although the conclusion was not definitive [33]. Conversely, the study by Currie et al. (2009) did not find any association between the use of insulin analogues and an increased risk of cancer compared to human insulin [49]. Smith et al. (2009) observed that although the evidence is insufficient for conclusions, this possibility must be subjected to surveillance, and more prospective studies in this area are needed [50].

A further preoccupation derived from the increased affinity for the IGF-1 receptor is the possibility of a faster evolution of retinopathy, perhaps up to threefold higher in patients using insulin glargine compared to those taking human insulin. Nevertheless, an analysis requested by the Food and Drug Administration (FDA) dispelled this concern, as reported by Smith et al. (2009) [50].

Despite the concern with the chronic complications of diabetes and the mitogenic effects attributed to insulin analogues, none of the analysed studies investigated their influence on such conditions. The systematic review performed by Plank et al. (2005) observed that other possible long-term undesirable effects have also not yet been studied [34]. We acknowledge that we have not fully discussed the safety of long-acting insulins. However, the study length of the clinical trials did not allow us to fully review these. Consequently, we are unable to comment further on the long term safety of insulin glargine

Given the increased use of insulin analogues in young females with T1DM, the safety profile of such drugs in pregnancy has paramount importance. However, none of the analysed studies included insulin-dependent pregnant women.

Despite the findings from the various reviews and health authority deliberations [14,16,18-20,23,44,45,47], there is growing use of long-acting insulins across countries and in this State [14,20,45,51]. This is despite the appreciably increased costs of insulin glargine versus NPH insulins. Potential reasons for the continued growth in their sales include marketing activities by pharmaceutical companies targeting healthcare providers; attractive devices for the administration of long-acting insulin analogues that facilitate application and entice patients; removal of less expensive insulin formulations from the market; and reduced weight gain [29]. Cohen and Carter (2010) in their review discussed the relationship between the increased use of long-acting insulins and the lack of evidence of increased effectiveness and improved safety of insulin glargine and NPH insulins [29].

From a methodological perspective, the assessed studies scored low, primarily between 0 and 2, which denotes poor methodological quality/high risk of bias. All studies were open-label, which are admittedly more prone to methodological bias.

Such methodological difficulties were justified by the authors, as the macroscopic physical differences among insulin formulations make blinding impossible with regard to both experimental subjects and investigators. However, blinding is recommended, at least when assessing the results or in the titration of doses, which has been rarely mentioned as having been performed in actual practice, as the method used for randomisation was not described.

In addition, Gill et al (2010) observed that the cost-benefit ratio of insulin glargine does not support its use, particularly in low income countries, although it might be indicated in specific conditions when there are sufficient resources [51].

Although studies reporting economic assessments were not the subject of this present systematic review, given the higher monthly cost and the lack of clear therapeutic advantages of insulin glargine compared to NPH insulin, the cost-effectiveness ratio seems to favour the use of the latter. For this reason, the manufacturer of insulin glargine should present the Unified Health System (SUS) managers with reasons justifying the higher cost of this drug, including any new evidence as well as more accurate assessments of its cost-effectiveness and impact on quality-adjusted life years (QALY) vs. NPH insulins. Otherwise, seek a price reduction to address concerns with the value of insulin glargine versus NPH insulins. This is because a recent UK study estimated potential savings of up to GB£625million over the decade with greater use of NPH insulins versus long-acting insulins [14]. The savings would

have been higher with a greater differential between the cost of the various insulins, e.g. insulin glargine in the UK is less than double the cost of NPH insulin [14], appreciably lower than the 536% differential seen in the State of Minas Gerais. If price reductions are not achieved, the authorities in the State of Minas Gerais should seek to delist insulin glargine from the state list of medicines. Both activities are in line with the activities already undertaken by the authorities in Germany. The alternative is to restrict the funding and use of long-acting insulins to second line, which is similar to the current situation in the UK [14, 20, 44]. However, this requires robust systems of physician monitoring and incentives to make sure the objectives of such initiatives are met; otherwise there will be disappointment [1, 2, 52-54]. Consequently, we believe the authorities should in the first instance seek price reductions from the manufacturers of insulin glargine to help the sustainability of the healthcare system in the State of Minas Gerais. This can be through discounts, rebates or price: volume agreements, which is similar to activities in other countries [2, 6, 26, 55-58].

We believe the findings of our systematic review, and its subsequent publication and ensuing debate, will help the authorities in the State of Minas Gerais achieve its aims. If there is delisting due to the reluctance by the manufacturers to appreciably lower the price of insulin glargine, we believe this review will provide the Judiciary with robust arguments and reasons to reduce the number of successful litigation cases brought by patients, which have been facilitated by pharmaceutical companies.

We acknowledge that our systematic review only went up to July 2009. However, we do not believe any more recent randomised controlled trials, if they have been performed and published, will have altered our conclusions given the number of existing papers demonstrating no statistically significant advantage for insulin glargine for reducing both hypoglycaemia episodes and HbA1c levels (Table 3).

## **CONCLUSIONS**

The present systematic review could not find any overall clinical benefits with insulin glargine compared to other investigated insulin formulations when glycaemic control and the frequency and severity of episodes of hypoglycaemia were analysed together. For these reasons, the SUS State Managers are advised to delist insulin glargine; alternatively, to negotiate a price reduction with the manufacturer to enhance its value. Publication of this

systematic review provides support for this decision as well as support to combat potential law suits if there cannot be satisfactory discussions.

## **LIST OF ABBREVIATIONS**

ANVISA - (Agência Nacional de Vigilância Sanitária) National Health Surveillance Agency

BMI - Body Mass Index

CFT - (Comissão de Farmácia e Terapêutica) Commission of Pharmaceuticals and Therapeutics

CGMS - continuous glucose monitoring system

CSII - continuous subcutaneous insulin infusion

FDA - Food and Drug Administration

HbA1c - glycated haemoglobin test

IGF-1 - insulin-like growth factor

IQWiG - Institute of Quality and Efficiency in Health Care, Germany

ITT - Intention to treat

QALY - quality-adjusted life years

SES/MG - (Secretaria de Estado de Saúde) State Health Secretary

SUS - (Sistema Único de Saúde ) National Public Health

T1DM - Type 1 Diabetes mellitus

## **Acknowledgements**

We thank the Minas Gerais State Health Secretary and the National Council for Scientific and Technological Development(CNPq) for funding this study. We also thank the Federal University of Minas Gerais for its support.

The authors declare that they have no conflict of interest that may have influenced this study.

No writing assistance was provided in the production of the manuscript.

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## Appendix 1 - Search strategy – Pub Med

Connector	Field	Parameter
	All fields	{Diabetes Mellitus Type 1} OR {Diabetes Mellitus tipo 1}
AND	All fields	{insulin glargine} OR {insulina glargina} OR {insulin NPH} OR {insulin NPH} {insulina regular} OR {insulin regular} OR {insulina NPH animal} OR {insulina regular recombinante} OR {insulin animal NPH} OR {insulin recombinant NPH} OR {insulina NPH recombinante} OR {insulina regular animal} OR {insulin animal regular} OR {insulin recombinant regular}
AND	All fields	Humans
AND	Language	{english} OR {spanish} OR {portuguese}
AND	All fields	{efficacy} OR {eficacia} OR {efetividade} OR {effectiveness} OR {cost-effectiveness}