Appendix 13 (as supplied by the authors): Adverse events (excluding hypoglycemia) reported in RCTs of long-acting insulin analogues in type 1 diabetes.

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Ashwell *et al.*, 2006[93]	IGlar+ILis: 2 patients (3.8%) with severe AEs NPH+HI: 4 patients (7.7%) with severe AEs	The AE profile was similar in the two groups. Of thses AEs, two events were considered by invetgator to be treatment-related. IGlar+ILis: one treatment-related AE was accidental insulin overdose NPH+HI: one treatment-related AE was urinary tract infection
Bolli *et al.*, 2006[98]	IGlar+ILis: NR NPH+ILis: NR	NR
Chase *et al.*, 2006[101]	IGlar+ILis: NR NPH (or lente) +ILis: NR	Possibly related AEs were comparable in both groups (NS)
Davies *et al.*, 2005[102]	IGlar+IAsp: NR NPH+IAsp: NR	NR
De Leeuw *et al.*, 2005[115]	IDet: 72.7% of patients in the first 6 months and 60.2% of patients in the 2nd 6 months experienced AEs; 12 severe AEs NPH: 76.8% in first 6 months and 69.7% in the 2nd 6 months; 6 severe AEs	IDet: CNS complaints (including migraine) were most frequent. Other AEs included retinal edema and macular degeneration, 3 moderate episodes of hyperglycemia, 2 patients with ketosis, and 1.9% of patients reported injection site reactions. NPH: vision disturbances were most frequent. Other AEs included retinal disorder, 2 patients with ketosis, and 1.0 % of patients reported injection site reactions.
Fulcher *et al.*, 2005[116]	IGlar: 277 events in 57 patients NPH: 241 events in 56 patients	Most common AEs were upper respiratory tract infections (IGlar: 7.2%; NPH: 11.2%), infections (IGlar: 7.2%; NPH: 6.2%), rhinitis (IGlar: 7.2%; NPH: 5.4%), headache (IGlar: 9.8%; NPH: 4.2%), and diarrhea (IGlar: 4.3%; NPH: 0.8%). Injection site reactions were similar (IGlar: 9 events in 5 patients; NPH: 7 events in 7 patients). Fewer than 5% of AEs were considered severe and fewer than 10% were considered related to study medication.
Garg *et al.*, 1998[114]	NPH+ILis NPH+HI	NR
Hermansen *et al.*, 2004[95]	IDet+IAsp NPH+HI	AEs were equally distributed between treatments. IDet+IAsp: 5 patients withdrew due to AEs; 3 events (hypoglycemia†, allergic reaction, and injection site reaction) were considered to be related to the trial products. NPH+HI: 1 patient withdrew due to AEs

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Hermansen *et al.*, 2001[117]	Approximately 30% of patients had AEs during either treatment period.	NR
Home *et al.*, 2005[119]	IGlar: 37/292 patients (13%) experienced AEs possibly related to study medication; 9% classified as serious NPH: 39/293 patients (13%) experienced AEs possibly related to study medication; 10% classified as serious	IGlar: 8 patients (3%) had injection site mass; 3 patients (1%) had injection site reaction NPH: 9 patients (3%) had injection site mass; 6 patients (2%) had injection site reaction Similar numbers of patients for each group developed a retinopathy severity level >61[Early Treatment Diabetic Retinopathy Study scale (ETDRS)], clinically significant macular edema and/or a 3-step progression on the ETDRS retinopathy scale.
Home *et al.*, 2004[120]	IDet: serious AEs reported for 14 patients (5%) NPH: serious AEs reported for 4 patients (3%)	AEs not considered to be related to study medication
Kawamura *et al.*, 2005[121]	IGlar+IAsp NPH+IAsp	NR
Kolendorf *et al.*, 2006[90]	IDet+IAsp: NR NPH+IAsp: 1 patient died from a myocardial infarction	Overall AE profile was similar between two groups and most events were mild and considered unrelated to trial products. 3 persons withdrew due to AEs.
Kudva *et al.*, 2005[122]	IGlar+IAsp UL+IAsp	NR
Mianowska *et al.*, 2006[100]	IGlar+(ILis or HI): NR NPH+ (ILis or HI): NR	No ketoacidosis occurred.
Murphy *et al.*, 2003[96]	IGlar+ILis: 21 treatment-emergent AEs in 13 patients; 1 pt with potential causally related AE NPH+HI: 29 treatment-emergent AEs in 15 patients; 1 pt with serious AE	Most of these events were mild and unrelated to insulin therapy. IGlar+ILis: The only potential causally related adverse event was transient pain in the injection site which was mild and did not necessitate discontinuation of the study insulin. NPH+HI: One SAE was that one pt required a 15-hour hospital admission during an episode of gastroenteritis.
Pesic *et al.*, 2006[107]	IGlar+IAsp: NR NPH (q.d.) +IAsp: NR NPH (b.i.d.) +IAsp: NR	NR

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Pieber *et al.*, 2007[141]	IDet+IAsp: 8.7% of patients reported SAEs IGlar+IAsp: 6.9% of patients reported SAEs	The overall frequency and severity of treatment-emergent adverse events was similar with twice-daily insulin detemir and once-daily insulin glargine.With the exception of 1 patient suffering from accidental injury and bone fracture, and one patient suffering from vomiting and cholelithiasis, all SAEs were single episodes occurring in a single patient, and most of the SEAs appeared unrelated to diabetes without any distinct pattern. 4 patients in each group had clinically significant changes in funduscopy/ fundus photography during the trial. IDet+IAsp: 1 of SAEs (hypoglycemic coma†) was probably or possibly related to treatment. 3 patients withdrew due to AEs (allergic reaction in the eyes, protruding intervertebral disc, and lumbar disc lesion). IGlar+IAsp: 4 of SAEs (proliferative retinopathy, hypoglycemic coma†, two incidences of hypoglycemia†) were probably or possibly related to treatment. 1 patient withdrew after development of proliferative retinopathy.
Pieber *et al.*, 2005[123]	Approximately 63% of all patients reported AEs IDet: 9 patients (3.3%) with serious AEs NPH: 2 patients (1.6%) with serious AEs	IDet: Only 1 serious AE considered to be related to study medication (1 transient ischemic attack); 4 patients experienced injection site reactions
Pieber *et al.*, 2000[112]	IGlar (HOE 901-30): 3 (3%) of patients with injection site reactions IGlar (HOE 901-80): 10 (9%) of patients with injection site reactions NPH: 3 (3%) of patients with injection site reactions	Only injection site reactions reported
Porcellati *et al.*, 2004[124]	NR	NR
Raskin *et al.*, 2000[113]	IGlar: Treatment-emergent AEs regardless of relationship to study medication occurred in 250/310 patients (80.6%) NPH: Treatment-emergent AEs regardless of relationship to study medication occurred in 236/309 patients (71.4%) in NPH group	Most common AEs were injection site events (occurring in 6.1% of IGlar patients and 0.3% NPH patients). Other AEs included headache and retinal events and increase in body weight. One NPH patient withdrew due to cancer of the pancreas.
Ratner *et al.*, 2000[125]	IGlar: 84.5% NPH: 86.7%	Only reported AEs were injection site reactions (15.2% in IGlar vs. 10.4% in NPH) and one fall in each group (due to hypoglycemia) resulting in serious events. Frequency and types of AEs similar in both groups.

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Robertson *et al.*, 2007[97]	IDet+IAsp: 837 AEs in 202 children (87%) NPH+IAsp: 436 AEs in 104 children (90%)	AEs were equally distributed between two treatments. The most frequest AEs in both groups were upper respiratory tract infection, headache, pharygitis, gastroenteritis, and influenza-like symptoms. AE type was similar in the two groups apart from injection site reactions (erythema, local pain, and swelling), which were more frequent with IDet. All injection site reactions were mild or moderate and reversible. IDet+IAsp: 11 events of injection site reactions in 8 (3.4%) children; 4 events of ketoacidosis for 4 children (1.7%) NPH+IAsp: 3 events of injection site reactions in 2 children (1.7%); 2 events of ketoacidosis for 2 children (1.7%)
Rosenstock *et al.*, 2000[126]	IGlar [30] +HI IGlar [80] +HI NPH+HI	Most frequent AEs considered related to study medication were injection site reactions.
Rossetti *et al.*, 2003[130]	IGlar (dinnertime) +ILis IGlar (bedtime) +ILis NPH (4 times/day) +ILis	NR
Russell-Jones *et al.*, 2004[133]	Less than 2% of patients reported serious AEs with probable/possible relation to treatment.	NR except for one episode of severe hyperglycemia in NPH group.
Schober *et al.*, 2002[134]	IGlar: 16 (9.2%) injection site reactions; 10 (5.7%) serious AEs; 4 (2.3%) systemic allergic reactions. NPH: 15 (8.6%) injection site reactions; 24 (13.7%) serious AEs; 2 (1.1%) systemic allergic reactions.	None of the allergic reactions was considered related to the study treatments. Other AEs reported were infection, upper respiratory tract infection, pharyngitis, rhinitis, and gastroenteritis. Injection site reactions were the only AEs considered related to treatment. Serious AEs included hyperglycemia and ketoacidosis.
Standl *et al.*, 2004[135]	IDet: 3 episodes of hyperglycemia due to missed doses; 4.5% of IDet patients had injection site reactions; 11.0% of patients experienced vision disorders; 5.2% retinal disorders. NPH: 0.7% of NPH patients had injection site reactions; 2 patients had abnormal fundoscopies after 12 months; 11.2% of patients experienced vision disorders; 8.2% retinal disorders.	AEs included hyperglycemia (due to missed doses), injection site disorders, abnormal fundoscopies, vision disorders, and retinal disorders.
Vague *et al.*, 2003[136]	Approximately 70% of patients in both groups had one or more AE IDet: 3 injection site reactions; one potentially allergic reaction to IDet NPH: One injection site reaction	Most common AEs were headache, upper respiratory tract infection, and rhinitis. Others included an allergic reaction to IDet and injection site reactions in both treatment groups. One patient in the IDet group withdrew due to headache, vomiting, and malaise (not considered to be treatment-related). One patient withdrew due to uterine carcinoma (not considered to be treatment-related).

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
White *et al.*, 2006[105]	IGlar+ILis: NR NPH (or lente) +ILis: NR	NR
Witthaus *et al.*, 2001[137]	IGlar+HI NPH+HI	NR

b.i.d.=twice a day; AE=adverse event; BMI=body mass index; CNS=central nervous system; DM=diabetes mellitus; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; q.d.=every day; RCTs=randomized controlled trials; SAE=serious adverse event.

*Citations of the studies are listed in the main article, available at www.cmaj.ca/cgi/content/full/180/4/385.

†Hypoglycemia could not be separated from other AEs.