

Appendix 14: Adverse events (excluding hypoglycemia) reported in RCTs of rapid-acting insulin analogues in type 2 diabetes.

Study*	Treatment arms	Description of adverse events
Altuntas <i>et al.</i> , 2003 ⁴⁹	ILis+NPH ILis+Metf HI+NPH	NR
Anderson, ³⁵ 1997	ILis+NPH or UL HI+NPH or UL	Flu syndrome, headache, infection, pain, pharyngitis, rhinitis, and surgery were reported by >5% of patients. There were no differences in AEs between the 2 groups
Anderson <i>et al.</i> , 1997 ³⁶	ILis+basal HI+basal	There was no difference in the frequency or type of AE between the two treatment groups. The most common AE were flu syndrome, pharyngitis, rhinitis, other infections, or headache. No local reactions in the injection site were reported in the pts treated with insulin lispro.
Boehm, ⁵⁰ 2004	BIAsp30 BHI30/70	IAsp: 90% of patients (458 events) experienced at least one AE, 11 of these possibly treatment-related; 15 patients (26%) experienced 19 cardiovascular events HI: 88% of patients (428 events) experienced at least one AE, 8 of these possibly treatment-related; 17 patients (25%) experienced 19 cardiovascular events
Bretzel, ³⁴ 2004	IAsp+NPH (bedtime) HI+NPH (bedtime) BHI30/70	Bronchitis and upper respiratory tract infections in >20% of patients on IAsp; >20% of patients on HI; 10% of patients on HI (70/30)
Chan <i>et al.</i> , 2004 ³³	ILis+NPH HI+NPH	Mild weight gain of 1.1 kg were observed at the end of the study, but there was no difference between the two arms (P=0.342)
Gallagher and Home, 2005 ⁵¹	IAsp+NPH HI+NPH	NR
Gallagher, ²³ 2007 (new)	IAsp HI	NR
Herz <i>et al.</i> , 2002 ³⁷	ILis Mix 25 Gly	NR
Herz <i>et al.</i> , 2003 ³⁸	ILis Mix 25 HI (30/70)	NR
Iwamoto, 2003 ⁵²	BIAsp30 BHI30/70	NR
Kilo, ⁵³ 2003	BIAsp30+ Metf NPH+Metf BHI30/70+ Metf	Upper respiratory tract infection was most common AE. One patient experienced blurred vision and pain in the extremities. BIAsp and BHI groups gained slightly more weight than NPH group. Total of 203 AEs reported for 87 (62%) patients. Upper respiratory tract infection in 21 patients.
Kokić <i>et al.</i> , 2003 ⁵⁴	Glim+Metf BHI30/70+ NPH ILis+Metf	NR
Kotsanos <i>et al.</i> , 1997 ³⁹	ILis HI	NR
Laube <i>et al.</i> , 1996 ⁵⁵	ILis HI	NR
Lourens, ⁵⁶ 2000	ILis Mix25 BHI30/70	Not reported except for slight weight gain in both arms.

Niskanen, ²⁰ 2004	BIAsp30 ILis Mix25	Incidence of AEs was similar in both groups URT infections & influenza-like symptoms were the most frequently reported ADRs (reported by > 5% of patients). Non of the serious ADE were judged to be related to trial products
Raskin, ⁶¹ 1999 [Abstract]	IAsp+NPH HI+NPH	Authors state majority of AEs were mild and considered unrelated to treatment; IAsp had slightly higher frequency of non-serious AEs
Roach, ⁴⁷ 1999	ILis Mix25 BHI30/70	No clinically significant differences between treatments with respect to incidence of AE.
Roach <i>et al.</i> , 1999 ⁴⁸	ILis Mix50 BHI50	No significant difference between treatments with respect to the incidence of adverse events.
Ross, ⁴¹ 2001	ILis+NPH HI+NPH	One patient required bilateral amputations above the knee. Body weight increased similarly in both groups.
Schernthaner, ³² 2004	ILis Mix50 BHI30/70	AEs reported by both groups were infection (7.5%), back pain (5.0%) and weight gain (5.0%). 2 serious AEs during run-in (not considered related to treatment). ILis: 11 patients (27.5%) had one or more AE HI: 14 patients (35.0%) had one or more AE; 4 serious (not considered related to treatment).
Vignati <i>et al.</i> , 1997 ⁴⁴	ILis+NPH HI+NPH	No significant differences in the number of treatment- or diseased-related adverse events for the two treatment groups.

ADR=adverse drug reaction; AE=adverse events; BIAsp=biphasic insulin aspart; BHI=biphasic human insulin; DM=diabetes mellitus; Glim=glimipiride; Gly=glyburide; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; Metf=metformin; Mix=premixed (biphasic) insulin; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SAEs=serious adverse events.

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