Insulin options in type 2 diabetes following market discontinuation of Mixtard® 30

Neil Munro, Marc Evans

Type 2 diabetes is a progressive condition that in many cases ultimately requires treatment with insulin to ensure good glycaemic control. A number of different insulins and regimens are available, allowing treatment to be tailored to an individual's therapeutic needs. Premixed human insulins are one option and are used by many people with type 2 diabetes. Novo Nordisk, the manufacturer of Mixtard® 30 (biphasic human insulin 30/70) has announced that, from the end of 2010, this insulin will no longer be available in the UK. This article offers practical solutions for switching people currently treated with Mixtard® 30 to other insulin treatment regimens, including human premixed insulins, analogue premixed insulins, long-acting basal insulins or a basal–bolus regimen.

Article points

1. Novo Nordisk, the manufacturer of Mixtard® 30 (biphasic human insulin 30/70), has announced that, from the end of 2010, this insulin preparation will no longer be available in the UK.
2. Affected individuals will need to be contacted and their current treatment requirements reassessed to inform the most appropriate treatment change.
3. Potential options include an alternative premixed human insulin preparation, premixed analogue insulin, human and analogue basal insulins (once or twice daily), basal–oral combinations, basal–bolus regimens or other combinations of insulins.

Key words
- Glycaemic control
- Insulin regimen
- Premixed insulin

Neil Munro is a GP in Surrey, an Associate Specialist in Diabetes in London and a member of the Diabetes Therapies Evaluation Network. Marc Evans is a Consultant Diabetologist at Llandough Hospital, Cardiff.

Premixed human insulin preparations are widely used by people with type 2 diabetes who are experiencing suboptimal blood glucose control with other diabetes treatments. Premixed insulins contain both rapid- and intermediate-acting components, which aim to target postprandial glucose (PPG) and fasting or preprandial glucose (FPG), respectively. *Table 1* lists the various human and analogue premixed insulins currently available in the UK.

Novo Nordisk, the manufacturer of Mixtard® 30 (biphasic human insulin 30/70), has announced that, from the end of 2010, this insulin preparation will no longer be available in the UK. Alternative insulin regimens will need to be discussed with people currently treated with this insulin. Several options are discussed in more detail below, with a particular focus on premixed insulins that have a similar ratio of rapid- and intermediate-acting insulin components to Mixtard® 30. This article examines the options when managing therapy changes for people with type 2 diabetes on Mixtard® 30. For those with type 1 diabetes on Mixtard® 30, it is recommended that alternative regimens be explored with local specialist diabetes teams.

Premixed human insulins

Clinical guidelines suggest that once- or twice-daily premixed human insulin may be considered at initiation of therapy, particularly if HbA_{1c} levels are ≥9.0% (≥75 mmol/mol) (NICE, 2009). A literature search did not reveal any clinical trials or observational studies describing a switch from Mixtard® 30 to other premixed human insulins. However, as the ratios of rapid- and intermediate-acting human insulin components are the same

with Mixtard® 30 and Humulin® M3 (biphasic human insulin 30/70; Eli Lilly, Basingstoke), clinical outcomes are expected to be similar. Readers should bear in mind that other premixed human insulin preparations are also available (Insuman® Comb 15, 25 and 50; Sanofi-Aventis, Guildford). One of these, Insuman® Comb 25 (biphasic human insulin 25/75), has a ratio of rapid- and intermediate-acting insulin components comparable to Mixtard® 30.

Premixed analogue insulins

Another option is to switch to a premixed analogue insulin. As the rapid-acting component of premixed analogue insulins is quickly absorbed from subcutaneous tissue, their time–action profile mimics that of physiological insulin secretion more closely than that of human premixed insulins (*Figure 1*). Unlike human insulin preparations, this allows premixed analogue insulins to be administered directly before or after a meal, and the flexibility this affords is particularly desirable for some people with type 2 diabetes. The three currently available premixed analogue insulins are listed in *Table 1*.

A systematic review by Qayyum et al (2008) analysed data from 16 studies comparing premixed human and analogue insulins. Overall, both types of premixed insulin decreased FPG and HbA_{1c} levels similarly, but premixed analogue insulins were more effective in decreasing PPG levels than premixed human insulins (Qayyum et al, 2008). As shown in *Figure 1*, better PPG control with premixed analogue insulins may be due to more rapid absorption and prompt dissociation of the fast-acting component compared with premixed human insulins (Hermansen et al, 2002; Coscelli et al, 2003).

In one crossover study of 61 people with type 2 diabetes, better PPG control was observed with NovoMix® 30 (biphasic insulin aspart 30/70; Novo Nordisk, Crawley) compared with Humalog® Mix25 (biphasic insulin lispro 25/75; Eli Lilly, Basingstoke) (Hermansen et al, 2002), which may be explained by a higher proportion of fast-acting insulin in the former. Similarly, it could be expected that Humalog® Mix50 (biphasic insulin lispro 50/50; Eli Lilly, Basingstoke) provides better PPG control than Humalog® Mix25 and NovoMix® 30, but no comparative studies exist.

Page points

1. Another option following market discontinuation of Mixtard® 30 is to switch to a premixed analogue insulin.
2. A systematic review by Qayyum et al (2008) analysed data from 16 studies comparing premixed human and analogue insulins. Overall, both types of premixed insulin decreased FPG and HbA_{1c} levels similarly, but premixed analogue insulins were more effective in decreasing PPG levels than premixed human insulins.

Table 1. Human and analogue premixed insulins.

Generic name	Trade name	Manufacturer	Composition	Onset of action	Peak activity	Duration of action
Human insulins						
Biphasic human insulin	Humulin® M3	Eli Lilly	30% soluble insulin 70% isophane insulin	30 min – 1 h	1–12 h	22 h
Biphasic human insulin	Insuman® Comb 15	Sanofi-Aventis	15% soluble insulin 85% isophane insulin	30 min – 1 h	2–4 h	11–20 h
Biphasic human insulin	Insuman® Comb 25	Sanofi-Aventis	25% soluble insulin 75% isophane insulin	30 min – 1 h	2–4 h	12–19 h
Biphasic human insulin	Insuman® Comb 50	Sanofi-Aventis	50% soluble insulin 50% isophane insulin	<30 min	1.5–4 h	12–16 h
Biphasic human insulin	Mixtard® 30	Novo Nordisk	30% soluble insulin 70% isophane insulin	<30 min	2–8 h	Up to 24 h
Analogue insulins						
Biphasic insulin lispro	Humalog® Mix25	Eli Lilly	25% lispro 75% lispro protamine	15 min	2 h	22 h
Biphasic insulin lispro	Humalog® Mix50	Eli Lilly	50% lispro 50% lispro protamine	15 min	2 h	22 h
Biphasic insulin aspart	NovoMix® 30	Novo Nordisk	30% aspart 70% aspart protamine	<10–20 min	1–4 h	Up to 24 h

The information presented in this table is taken from the summary of product characteristics (SPCs) for each product.
SPCs can be found by searching for the product name at www.medicines.org.uk/emc.

In terms of intermediate outcomes, Qayyum et al (2008) also found that premixed human and analogue insulins were associated with similar levels of weight gain. Data from a meta-analysis (Davidson et al, 2009) specifically assessing hypoglycaemia rates demonstrate that there is a lower risk of major events with NovoMix® 30 than with Mixtard® 30 (odds ratio, 0.45; 95% confidence interval, 0.22–0.93; $P<0.05$), which is due to differences in the pharmacokinetic profiles of these agents (*Figure 1*). There was a paucity of data from large randomised controlled trials comparing Humalog® Mix25 with premixed human insulins; however, a literature review suggested that the incidence of major and minor hypoglycaemic events was similar between these treatments (Garber, 2006).

In a crossover comparison of three-times daily Humalog® Mix50 and twice-daily biphasic human insulin 30/70 in 40 people with type 2 diabetes, there were no significant differences in the incidence of hypoglycaemia (Schernthaner et al, 2004).

Other insulin treatment regimens

One disadvantage of premixed treatment regimens is that it is not possible to independently vary the dose of the constituent insulins. Therefore, for some people (particularly older people for whom hypoglycaemia is unacceptable, or for those reluctant to start a complex insulin-based treatment regimen) combination therapy with a long- or intermediate-acting insulin and oral antidiabetes agents may be an alternative. However, it should be noted that moving to a basal insulin in combination with an oral antidiabetes agent such as metformin, a sulphonylurea or a thiazolidinedione would no longer address PPG excursions.

For other people, such as those with unpredictable lifestyles, a switch to a basal–bolus or "basal plus" regimen (where a basal insulin regimen is combined with one to three mealtime bolus injections) may be appropriate. A summary of suggested treatment regimens according to patient characteristics is shown in *Table 2*.

NICE (2009) guidance offers the option of initiating people with type 2 diabetes on neutral protamine Hagedorn (NPH) insulin but also permits use of long-acting analogue insulin (such as glargine or detemir). To the authors' knowledge, there are no data investigating a switch from premixed human insulin to the long-acting basal analogue insulin detemir or to intermediate-acting NPH insulin, although some comparative data were found for insulin glargine. In insulin-naïve people with type 2 diabetes, adding a once-daily dose of insulin glargine to oral antidiabetes agents improved glycaemic control more effectively, and with less hypoglycaemia, than treatment with twice-daily biphasic human insulin 30/70 alone (Janka et al, 2005).

A recent, large, long-term, randomised controlled study (4T; Treating to Target in Type 2 Diabetes) provided data that may inform clinical decisions when switching people currently using Mixtard® 30 to an alternative regimen (Holman et al, 2009). Briefly, 4T sought to assess the efficacy and safety of various analogue insulin-based regimens in people with type 2 diabetes who required initiation of insulin therapy. The trial assessed premixed, prandial bolus and basal insulin treatment regimens as initial add-on therapy to metformin and a sulphonylurea, with subsequent intensification as required.

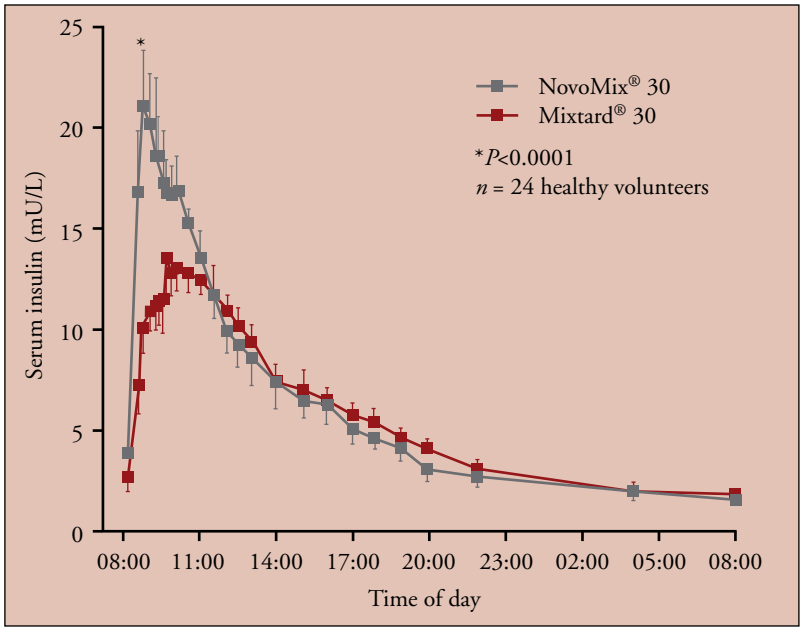

Figure 1. Actual serum insulin profiles in healthy volunteers after a single injection of either NovoMix® 30 (0.2 U/kg) or Mixtard® 30 (0.2 IU/kg). Reproduced with permission from Jacobsen et al (2000) © Springer 2000.

At the end of the study, HbA_{1c} levels were similar across treatment groups; however, compared with the other regimens investigated, starting with basal and intensifying with prandial insulin was associated with the least weight gain or hypoglycaemia (Holman et al, 2009).

Practical considerations when switching treatment regimens from Mixtard® 30

In order to identify people currently receiving Mixtard® 30, it will be necessary to search the practice database. Affected individuals will need to be contacted and their current treatment requirements reassessed to inform the most appropriate treatment change. From a practical point of view, the following points should be considered when agreeing on the best alternative option.

- Due account needs to be taken of the variable responsiveness of individuals to insulin preparations when making dose adjustments. As a result, it is important that blood glucose levels are self-monitored before, during and after the switch period. Close attention to these data will help in ensuring successful conversion.
- For individuals who prefer injecting insulin immediately before a meal, who experience problematic hypoglycaemia or have marked elevations in blood glucose after meals, NICE (2009) recommends treatment with premixed preparations that include short-acting analogue insulins (*Table 1*).
- People using premixed insulin once or twice daily should be monitored for the need for a further pre-meal injection or for an eventual change to a mealtime plus basal insulin regimen, based on human or analogue insulins, if blood glucose control remains inadequate (NICE, 2009).
- While premixed human insulins must be injected 30 min before a meal, the premixed analogue insulins NovoMix® 30, Humalog® Mix25 and Mix50 may be injected shortly before (0–15 min) or soon after a meal (Electronic Medicines Compendium [EMC], 2009a; 2009b). This flexible injection timing relative to meals is thought to improve adherence and quality of life compared with premixed human insulin (Dunn and Plosker, 2002; Garber et al, 2007).
- The summary of product characteristics (SPC) for NovoMix® 30 suggests that, when transferring a person from premixed human insulin, it is possible to initially transfer with the same dose and regimen and then titrate the doses according to the individual's PPG levels (EMC, 2009a). Nevertheless, a more cautious approach may be appropriate in particular circumstances. It is important to always adopt

Page points

1. In order to identify people currently receiving Mixtard® 30, it will be necessary to search the practice database. Affected individuals will need to be contacted and their current treatment requirements reassessed to inform the most appropriate treatment change.
2. For individuals who prefer injecting insulin immediately before a meal, who experience problematic hypoglycaemia or have marked elevations in blood glucose after meals, NICE recommends treatment with premixed preparations that include short-acting analogue insulins.
3. People using premixed insulin once or twice daily should be monitored for the need for a further pre-meal injection or for an eventual change to a mealtime plus basal insulin regimen, based on human or analogue insulins, if blood glucose control remains inadequate.

Table 2. Insulin choices for people currently receiving Mixtard® 30.

Characteristic	Treatment regimen			
	Human premixed insulin	Analogue premixed insulin	Basal insulin only	Basal + bolus insulin
Preference for fewer injections	X	X	X	
Variable meal pattern				X
Variable daily routine				X
Limited capability (e.g. dexterity, cognitive function)	X	X	X	
Better PPG control required		X		X
Unwilling to self-monitor blood glucose several times daily	X	X		
Problematic hypoglycaemia		X	X	
Limited support from family and GP	X	X	X	

PPG = postprandial glucose; X = Preferred choice
Reproduced and adapted with permission from Barnett et al (2008) © John Wiley and Sons 2008.

Page points

1. In older people with type 2 diabetes, in addition to achieving individualised HbA_{1c} targets, avoiding hypoglycaemia is paramount and the choice of insulin regimen should reflect this aim.
2. Following the discontinuation of Mixtard® 30, clinical decisions regarding subsequent treatment steps should be individualised.
3. It is important to discuss all available options with each person and to reassure them that their standard of care will not be altered.

an individualised approach to diabetes therapy and, in particular, changes in insulin regimen. Clearly, this also applies when converting Mixtard® 30 users to other premixed insulin preparations.

- If a switch to NovoMix® 30 is considered, many people can use the same insulin pen device; however, those using InnoLet® (Novo Nordisk, Crawley) will be unable to administer NovoMix® 30 with this device and an alternative will need to be discussed. Readers should note that Levemir® (insulin detemir; Novo Nordisk) is available for use with InnoLet®.
- When transferring a person with type 2 diabetes from Mixtard® 30 to a basal insulin, it is possible to start with the basal dose from the premixed human insulin and titrate upwards according to results from serial blood glucose measurements.
- If a basal–bolus regimen is required, switching could be achieved by initiating the individual on a basal dose equivalent to the existing premixed human insulin basal dose and subsequently calculating the required prandial component using self-monitored blood glucose data. Alternatively, for people who have limited support from their family or healthcare professionals, an intermediate solution may be the basal-plus regimen (Barnett et al, 2008).
- There will be a subset of people with type 2 diabetes for whom supply of insulin in vials is an important consideration, such as residents of care homes. Readers should be aware that some of the insulins that may be used as an alternative to Mixtard® 30, such as NovoMix® 30 and Humalog® Mix50, are not available in vials.
- In older people with type 2 diabetes, in addition to achieving individualised HbA_{1c} targets, avoiding hypoglycaemia is paramount and the choice of insulin regimen should reflect this aim.

Conclusion

Following the discontinuation of Mixtard® 30, clinical decisions regarding subsequent treatment steps should be individualised. Treatment should be tailored to the needs and circumstances of the person with diabetes; potential options include an alternative premixed human insulin preparation, premixed analogue insulin, human and analogue basal insulins (once or twice daily), basal–oral combinations, basal–bolus regimens or other combinations of insulins. It is important to discuss all available options with each person and to reassure them that their standard of care will not be altered. ■

For further information regarding the discontinuation of Mixtard® 30 and the resources and services available to help healthcare professionals manage their Mixtard® 30 patients, please contact your local Novo Nordisk representative or call 0845 600 5055.

If you have any comments about this article, please contact the editorial team by email at dpc@sbcommunications group.com or call 0207 627 1510.

Disclosures

The authors are grateful to Watermeadow Medical for medical writing support, funded by Novo Nordisk. Neil Munro has received fees for serving as a speaker, a consultant or an advisory board member for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, LifeScan, Medtronic, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sankyo, Servier, and Takeda. Marc Evans serves as a consultant to Abbott, Allergan, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, MSD, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Takeda.

Publisher's note

The usual journal style of using generic rather than brand names for medicines has not been applied in this article to enhance readability.

Barnett A, Begg A, Dyson P et al (2008) *Int J Clin Pract* **62**: 1647–53

Coscelli C, Iacobellis G, Calderini C et al (2003) *Acta Diabetol* **40**: 187–92

Davidson JA, Liebl A, Christiansen JS et al (2009) *Clin Ther* **31**: 1641–51

Dunn CJ, Plosker GL (2002) *Pharmacoeconomics* **20**: 989–1025

Electronic Medicines Compendium (2009a) *NovoMix® 30 Summary of Product Characteristics.* Available at: http://tiny.cc/oo3de (accessed 27.05.10)

Electronic Medicines Compendium (2009b) *Humalog® Mix25 and Mix50 Summary of Product Characteristics.* Available at: http://tiny.cc/aq0sr (accessed 27.05.10)

Garber AJ (2006) *Drugs* **66**: 31–49

Garber AJ, Ligthelm R, Christiansen JS, Liebl A (2007) *Diabetes Obes Metab* **9**: 630–9

Hermansen K, Colombo M, Storgaard H et al (2002) *Diabetes Care* **25**: 883–8

Holman RR, Farmer AJ, Davies MJ et al (2009) *N Engl J Med* **361**: 1736–47

Jacobsen LV, Søgaard B, Riis A (2000) *Eur J Clin Pharmacol* **56**: 399–403

Janka HU, Plewe G, Riddle MC et al (2005) *Diabetes Care* **28**: 254–9

NICE (2009) *Type 2 Diabetes: Newer Agents (Partial Update of CG66).* NICE, London. Available at: http://tinyurl.com/32wvwqa (accessed 26.05.10)

Qayyum R, Bolen S, Maruthur N et al (2008) *Ann Intern Med* **149**: 549–59

Schernthaner G, Kopp HP, Ristic S et al (2004) *Horm Metab Res* **36**: 188–93