Insulin is a life-saving treatment for patients who have type 1 diabetes mellitus. Without insulin these individuals would develop severe hyperglycaemia — resulting in ketosis, ketoacidosis, coma and subsequent death. The management of type 1 diabetes with insulin aims to:

- Control the symptoms of hyperglycaemia
- Prevent diabetic ketoacidosis, an acute and life-threatening complication of hyperglycaemia
- Prevent microvascular complications (retinopathy, nephropathy and neuropathy)
- Avoid the development of macrovascular complications (cardiovascular and peripheral vascular problems) in later life

The type of insulin and treatment regimen used by patients with type 1 diabetes depends on many factors, including: patient preference; lifestyle; eating patterns; the insulin device used; the level of glycaemic control required by the patient; his or her ability to self-monitor; and the risk or previous history of hypoglycaemia. This article explains the treatment options available to adult patients and discusses the main issues surrounding the use of insulin to manage type 1 diabetes.

Treatment regimens

The aim of insulin therapy is to try to mimic normal physiological insulin release from the pancreas. To achieve
this, multiple daily injections — often referred to as basal-bolus regimens — are commonly used. These regimens involve injecting a long- or intermediate-acting insulin once or twice a day, plus a bolus injection of a short-acting insulin before each meal. The bolus insulin injections control post-prandial peaks in glucose levels and the daily insulin injections regulate basal hepatic glucose output. Additional bolus doses may be needed if snacks that are high in carbohydrate are eaten between meals.

A mixture of short- and long-acting insulin in a fixed-dose preparation can be used as an alternative to the basal-bolus regimen. This is known as a biphasic regimen and is usually injected twice a day.

It is important to note that these regimens do not accurately mimic physiological insulin release. This is because insulin is injected into the peripheral circulation, rather than the portal circulation, and because exogenous insulin concentrations are adjusted crudely and not on a continuous basis as would happen in normal physiological processes.3

Other regimens, such as basal-only, or basal-plus (injecting daily basal insulin plus one single injection with a main meal), can be useful in type 2 diabetes. These regimens are not routinely used for patients with type 1 diabetes because they do not deliver sufficient glycaemic control.

Types of insulin

Insulin can be derived from animals (ie, porcine or bovine) or humans, or analogues of insulin can be synthesised. Insulin is a polypeptide hormone with a complex structure (see Figure 1). Each type of insulin differs in terms of its exact amino-acid sequence. Human sequence insulin can be produced semisynthetically by enzymatic modification of porcine insulin or biosynthetically using recombinant DNA technology.4 Animal-sourced insulin is no longer commonly used in the UK and has largely been replaced by human insulin and insulin analogues. The main types of insulin are classified as rapid/short-acting, intermediate-acting, long-acting and biphasic. The onset of action, peak activity and duration of action of each product differs (see Box 1) and they are all subject to interpatient variability.

Rapid/short-acting insulin

Insulin aspart (Novorapid), insulin lispro (Humalog) and insulin glulisine (Apidra) are examples of insulin analogues commonly used in the UK. They are often referred to as rapid-acting insulin analogues because they have a quicker onset of action than short-acting human soluble insulins and have a shorter duration of action.

Examples of commonly used short-acting insulins are the brands Actrapid and Humulin S. The rapid-acting insulin analogues and short-acting insulins should be administered before meals to control blood glucose levels during and after eating.

The main advantage of the rapid-acting insulin analogues over short-acting insulins is the reduced risk of severe hypoglycaemia (by up to 30%) associated with their use. Another advantage of rapid-acting insulin analogues is that they can be injected just before a meal (short-acting insulin needs to injected about 30 minutes before a meal).3 However, they are more expensive than the short-acting insulins and demonstrate no real benefits to overall glycaemic control. Although rapid-acting insulin analogues are often used in preference to short-acting insulins in the UK, the National Institute for Health and Care Excellence advises that they should only be used as an alternative to meal-time soluble insulin if

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<td>Biphasic</td>
<td>Biphasic insulin aspart (Novomix 30)</td>
<td>10–90 minutes</td>
<td>2–4 hours</td>
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Figure 1: Polypeptide structure of insulin
Expanded broad-spectrum coverage is on your side

TYGACIL has *in vitro* activity against a wide range of pathogens\(^1,2\)

For the treatment of complicated intra-abdominal infections (cIAI) and complicated skin and soft tissue infections (cSSTI) excluding diabetic foot infections\(^2\)

Tygacil should be used only in situations where it is known or suspected that other alternatives are not suitable\(^2\)

References:
**Abbreviated Prescribing Information**

**JIL (Tigecycline). See Summary of Product Characteristics (SPC) before Prescribing.**

**Indication:** Tygacil 50mg Powder for Solution for Infusion (or for infusion). Each 5ml Tygacil vial contains 50mg of tigecycline. After reconstitution, 1ml contains 10mg of tigecycline.

**Actions:** Tygacil is indicated in adults for the treatment of cuffed skin and soft tissue infections (cSSTI), excluding cutaneous infections and complicated intra-abdominal infections. Tygacil should be used only in situations where it is known or suspected that other alternatives are not suitable. Consideration should be given to official guidance on the appropriate use of bacterial agents. **Dosage:** (Intravenous infusion only over 30 to 60 minutes): The recommended dose for adults is an initial dose of 250mg followed by 125mg every 12 hours for 5 to 14 days. The number of therapy should be guided by the severity, site of infection, and a patient’s clinical response. Hepatic Insufficiency: In patients with hepatic impairment (Child Pugh C), the dose of Tygacil should be reduced to 25mg every 12 hours following the 100mg dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. Renal Insufficiency: No dosage adjustment is necessary for patients with renal impairment or patients undergoing dialysis. Elderly patients: No dosage adjustment is necessary for elderly patients. Paediatric population: The safety and efficacy of tigecycline in children below 18 years have not yet been established.

**Indications:** Hypersensitivity to the active substance or to any excipients. Patients hypersensitive to tetracycline derivatives may be hypersensitive to tigecycline. **Special Warnings and Precautions:** In clinical studies in cSSTI, cIAI, diabetic foot ulcers, nosocomial pneumonia and studies in resistant staphylococcus, a numerically higher mortality rate among Tygacil patients has been observed as compared to the comparator arm. The causes of these findings remain unknown, but efficacy and safety studies on the comparators cannot be externally validated. In clinical trials in cIAI patients, impaired healing of the wound has been associated with superinfection. Patients who develop super-infections, for example nosocomial pneumonia, appear to be associated with outcomes. Patients should be closely monitored for the development of super-infection. The use of Tygacil in non-approved indications is not recommended. Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline. Cases of liver injury with a predominantly cholestatic pattern have been reported in patients receiving tigecycline treatment, including some cases of hepatic failure with a fatal outcome. Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effect profiles. Acute pancreatitis, which can be serious, has occurred following association with tigecycline treatment. Combination antibiotic therapy should be considered in patients with clinically apparent intestinal perforation or patients with incipient sepsis or septic shock. In case of severe, persistent diarrhea, the possibility of antibiotic-induced life-threatening pseudomembranous colitis may be taken into consideration. Experience in the use of tigecycline treatment of infections in patients with severe underlying diseases is limited. **Drug Interactions:** See SPC. **Pregnancy:** Beware of potential risks during pregnancy. **Lactation:** Tigecycline should not be used during pregnancy and lactation unless clearly necessary. **Side Effects:** Very common: Nausea, vomiting, diarrhoea. Common: Pneumonia, abscesses, infections, prolonged prothrombin time (PT), prolonged prothrombin time (PT), hypoglycaemia, dizziness, phlebitis, abdominal pain, dyspepsia, anorexia, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), hyperbilirubinaemia, pruritus, rash, headache, impaired hearing, elevated amylase, increased blood urea nitrogen (BUN), overdrive. Intravenous administration of tigecycline at a single dose of 300mg over 60 minutes resulted in an increased incidence of nausea and vomiting. **Presentation:** 5ml clear glass vials with snap aluminium crimp seal. Tygacil is distributed in a ten vial tray p pads.

**Legal Category:** POM **Basic NHS Price:** £323.10 **Number:** EU/1/06/336/001 **Marketing Authorisation Holder:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

Further information is available on request from Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. **Date of Revision:** 28th August 2012

Ref: TL 4_0

Adverse events should be reported. Reporting forms and instructions can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.
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nocturnal, or late inter-prandial, hypoglycaemia is a problem — or if the patient needs or desires adequate blood glucose control without the use of snacks between meals (and this is needed or desired).7

**Intermediate-acting insulins** Intermediate-acting insulins may also be referred to as isophane or neutral protamine Hagedorn (NPH) insulins. They are a cloudy, insulin-containing, white crystalline precipitate of isophane insulin and require mixing before administration. They have an intermediate duration of action, are given once or twice a day and do not need to be co-ordinated with meals. Examples include Insulardard and Humulin I.

If isophane insulin is administered at bedtime, then a peak in insulin activity will occur overnight when glucose levels are low — increasing the risk of nocturnal hypoglycaemia. Concerns about this can prevent patients from achieving optimal glucose control, because they tend to use lower doses of insulin at night to prevent hypoglycaemia occurring.

This type of insulin is normally used as part of a basal-bolus regimen with a rapid or short-acting insulin.

**Long-acting insulin** Insulin glargine (Lantus) and insulin detemir (Levemir) are human insulin analogues that have a prolonged duration of action. They are usually administered once daily but can be used twice a day if needed. Insulin degludec (Tresiba) has recently been launched and has a longer duration of action than insulin glargine and insulin levetir. NICE recommends that long-acting analogue insulins should be considered if:

- Nocturnal hypoglycaemia is a problem when using isophane insulin
- Morning hyperglycaemia occurs when using isophane insulin, which makes daytime blood glucose control difficult
- Rapid-acting insulin analogues are used for mealtime blood glucose control

**Biphasic insulins** Biphasic insulins contain a mixture of a rapid or short-acting insulin and an intermediate-acting insulin. The rapid or short-acting component covers the post-prandial rise in blood glucose, and the intermediate-acting component provides basal glycaemic control.

Examples of human biphasic insulins are Humulin M3 and the Insulan Comb range. They are usually injected twice daily (approximately 30 minutes before a meal).

There are a number of analogue pre-mixed insulins, eg, Humalog Mix25, Humalog Mix50 and Novomix 30. These insulins should be administered twice a day just before a meal.

NICE recommends that twice-daily insulin regimens should be used by those individuals for whom keeping the number of daily injections at a minimum is an important factor in their quality of life. These twice-a-day regimens can also help people who find adherence to lunchtime insulin injections difficult, or for adults with learning difficulties who may require assistance from others. Biphasic rapid-acting insulin analogues can also be a suitable option for those who are prone to experiencing nocturnal hypoglycaemia.

**Delivering insulin** There is a range of devices that can be used by patients to subcutaneously inject themselves with insulin. Patients can withdraw insulin from a vial using an insulin injector pen; alternatively they can use an insulin injector pen, which can be either refilled using insulin cartridges or is prefilled and disposable.

The insulin injector pens display the amount of insulin in units and the dose to be injected is “dialled up”, by twisting the device. Most pens have a audible click when the dial is turned, allowing visually impaired patients to count the clicks to dial up the required insulin dose. It is important that patients are always given the correct insulin device, because insulin doses may be missed or inaccurate if a patient is unfamiliar with the device and unable to use it.

Good awareness of insulin safety is also important for all those involved with insulin administration (see Box 2).

Insulin pumps deliver a varied dose of rapid- or short-acting insulin continuously at a pre-set rate. When patients eat, they press a button on the pump to deliver an extra bolus dose of insulin. The pump has a reservoir holding enough insulin for two to three days. The insulin is delivered through a fine tube that runs from the pump to a subcutaneous cannula (usually inserted around the abdomen). The cannula can be left in place for two to three days before needing to be replaced and repositioned. The pump is battery operated and indicates to the user when it is low in energy.

Patients using insulin pumps will need support from a specialist team, which usually includes a doctor, a diabetes specialist and a dietitian; together they ensure patients have the skills necessary to operate the pump and to determine their required doses accurately. NICE recommends insulin pump therapy for adults and children aged 12 years and older with type 1 diabetes, provided that attempts to achieve target HbA1c with multiple daily injections have resulted in disabling hypoglycaemia. Insulin pump therapy is also recommended If HbA1c has remained high (over 69mmol/mol) with multiple daily injections (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.7

**Other treatment options** Whole-organ pancreatic transplantation for the treatment of type 1 diabetes has largely been reserved for

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**Box 2: Insulin safety**

There were 3,881 wrong insulin dose incidents reported to the National Patient Safety Agency between 2003 and 2009. These included one death and one incident of severe harm caused by 10-fold dosing errors as a result of abbreviating the word “unit”. Three deaths and 17 other incidents involved the incorrect use of intravenous syringes for the measurement and administration of insulin. The NPSA sent out a rapid response alert in 2010 to address the main types of error and avoid further incidents.

In 2011 the NPSA issued a second alert recommending that all adult patients on insulin therapy should receive a patient information booklet and an “insulin passport” to help provide accurate identification of the insulin products they are using and to ensure this essential information is shared between different healthcare settings.
those undergoing renal transplantation for end-stage diabetic nephropathy. Although normalisation of glycaemic control is achieved following successful transplantation, this option carries the burden of ongoing immunosuppressive medication and the risk of pancreatic graft rejection.1

Experimental islet cell transplantation may be a promising treatment option for patients with type 1 diabetes. β-Cells isolated from a donor pancreas are injected into the portal venous system where they then lodge within liver sinusoids. These β-cells remain sensitive to glucose and secrete insulin into the portal system in the same way as normal physiological systems.5

Monitoring
It is not possible to standardise the frequency of blood glucose monitoring for all patients with type 1 diabetes because this will be different for each patient. Training on how to test levels and the interpretation of results should be undertaken by all patients as part of a structured education programme (see below).

There are many factors that determine the frequency of self blood glucose monitoring, such as driving status, the level of control required, patient preference, risk of hypoglycaemia and illness (during times of illness a period of more frequent monitoring may be needed).

The type of insulin regimen is also important. For example, it would be expected that more frequent blood glucose monitoring is required for basal-bolus and insulin pump-treated patients — especially for those who have been taught to adjust their doses according to their mealtime calorie intake — than for those on insulin mixes. The optimal targets for capillary blood glucose levels are a pre-prandial blood glucose level of 4–7mmol/L and a post-prandial blood glucose level of less than 9mmol/L.5

Continuous glucose monitoring is a method that can be used to provide a detailed picture, over a number of days, of blood glucose levels. It tends to be reserved for patients who are struggling with erratic glycaemic control or experiencing hypoglycaemia, because it can help identify patterns in blood glucose control.

Long-term blood glucose control can be monitored by measuring HbA1c. Keeping this value within a certain range (see Box 3) can help prevent the long-term complications of diabetes.

Patients should also be taught how to test themselves for urinary or blood ketones to help avoid diabetic ketoacidosis, eg, during times of illness.

Treatment-related complications
Hypoglycaemia
Hypoglycaemia is defined as a blood glucose level of less than 4mmol/L. It is a common side effect of insulin treatment and can cause considerable anxiety for some patients, affecting their quality of life. People with type 1 diabetes experience approximately two episodes of mild hypoglycaemia each week7 and several large studies have reported the annual prevalence of severe hypoglycaemia to be 30–40%.5

Most people will notice warning signs when their blood glucose level starts to fall (although some patients can lose this ability). These warning signs will vary between individuals but can include:9

- Feeling hungry
- Trembling or shakiness
- Sweating
- Anxiety or irritability
- Going pale
- Fast pulse or palpitations
- Tingling of the lips
- Sweating
- Trembling or shakiness
- Feeling hungry
- Fast pulse or palpitations
- Tingling of the lips
- Sweating

Signs of a more severe hypoglycaemic episode can include difficulty in concentrating, vagueness or confusion and irrational behaviour.

Current recommendations are to treat an episode of hypoglycaemia immediately with 15–20g of a short-acting carbohydrate such as:9,10

- Three or four heaped teaspoons of sugar dissolved in water
- Four or more glucose tablets
- Five sweets, eg, jelly babies
- 120ml glass of non-diet soft drink, eg, cola or lemonade
- 150–200ml glass or carton of fruit juice
- Three or four heaped teaspoons of sugar dissolved in water
- Glucose gel

Skin-related effects
Repeated use of the same injection site increases the risk of lipoatrophy (localised loss of adipose tissue under the skin) and lipohypertrophy (lump under the skin caused by accumulation of extra adipose
tissue). Lipohypertrophy is the most common cutaneous complication associated with insulin therapy. Areas affected by lipoatrophy or lipohypertrophy will become relatively pain-free to inject into — causing patients to use these areas more often. However, the absorption of insulin from these lipodystrophic areas can be erratic and lead to frequent difficulties in achieving ideal blood glucose control. The likelihood of lipodystrophy can be reduced by regular rotation of injection sites.1

Education
A diabetes education programme, covering all the major components of diabetes self-care, should be offered to all adults with type 1 diabetes in the months after diagnosis — and periodically thereafter according to need.1 There are several structured courses available, such as the “dose adjustment for normal eating” (DAFNE) programme and the “Bournemouth insulin dose adjustment course” (known as BERTIE for patients and BIDAC for health professionals).

References