# Shared care guideline

# Humulin R® U500 insulin for patients with severe insulin resistance

## 1 Scope

For prescribing by general practitioners (GPs).

## 2 Purpose

To provide advice on the safe prescribing Humulin R® U500 insulin for patients with severe insulin resistance.

## 3 Introduction

In the UK insulin is usually formulated at a concentration of 100 units per ml. **Humulin R® U500** insulin is a concentrated formulation of insulin (500 units per ml).

Patients with severe insulin resistance may have significantly higher insulin dose requirements than other patients with diabetes. The insulin dose can often reach more than 200 and up to 2000 units per day. Each insulin dose then requires two or three injections as the maximum insulin that can be injected in one injection is about 50 units. Large volumes injected subcutaneously may affect the pharmacokinetics of the insulin. Large volume and multiple injections can also cause discomfort and lead to poor compliance and poor glycaemic control.

**Humulin R® U500** insulin should be considered for patients who require large doses of insulin (usually above 200 units per day) as this can reduce the volume of injected insulin, improve compliance, and can lead to improvements in glycaemic control (HbA1c).

## 4 Shared care

Sharing of care assumes communication between the specialist, GP and the patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

# 5 Shared care responsibilities

## 5.1 Consultant

The decision to start **Humulin R® U500** insulin will be made by a consultant physician at the national severe insulin resistance service at Addenbrooke's Hospital. A copy of the shared care guidelines will be sent to the GP. If the GP has any queries about the prescribing of **Humulin R® U500**, they should contact the relevant hospital specialist as soon as possible.

The consultant and the national severe insulin resistance team will:

- Educate the patient fully regarding safe administration, dosing schedule and storage of **Humulin R® U500** insulin, and provide guidance to the patient on appropriate blood glucose monitoring.
- Provide the patient with written information regarding safe administration, dosing schedule and storage of **Humulin R® U500** insulin and guidance in dealing with hypoglycaemia, concurrent illnesses and hospital admission.
- Provide a labelled box for storage of **Humulin R® U500** and 0.5ml insulin syringes.
- Send a letter to the GP requesting shared care for this patient.
- Provide clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance documenting current dose and most recent blood results.
- Evaluate any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment with **Humulin R® U-500** insulin where necessary.
- Inform GP of patients who do not attend clinic appointments.
- Ensure that backup advice for the patient and GP is available.
- Inform hospital pharmacist about any new patients starting on **Humulin R® U500** insulin.
- Liaise with the patient's usual community pharmacy (or dispensing GP surgery) regarding sourcing and safe dispensing of **Humulin R® U500** insulin.

## 5.2 Hospital pharmacy

Provide initial supplies of **Humulin R® U500 for a maximum of three months.**

## 5.3 General practitioner

- Monitor patient's overall health and well being.
- Prescribe the **Humulin R® U500** insulin.
- Prescribe glucose monitoring strips as required.
- Report any adverse events to the hospital specialist, where appropriate.

### 5.4 Patient

- Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any queries.
- Check that the specialists have provided a patient-held record or information sheet to alert other clinical staff to the treatment they are receiving.
- Share any concerns they have in relation to treatment with **Humulin R® U500** insulin.
- Report any adverse effects to their specialist or GP whilst taking **Humulin R® U500** insulin.
- Report to the specialist or GP if they do not have a clear understanding of their treatment.
- Participate in the monitoring of blood glucose, to assist health professionals to provide effective, safe, appropriate treatment.
- Inform relevant health professionals of the use of **Humulin R® U500** insulin at every contact and during any admission to hospital.

## 6 Dose and administration

**Humulin R® U500** insulin is a polypeptide hormone structurally identical to human insulin synthesized through rDNA technology in a laboratory strain of *Escherichia coli* bacteria. **Humulin R® U500** insulin is not modified by any agent that might alter its duration of action. Clinical experience has shown that it takes effect within 30 minutes, has a peak similar to that observed with regular human insulin (100units/ml) and has a relatively long duration of activity following a single dose (up to 24 hours) as compared with regular insulins (100units/ml). This effect may be due to the high concentration of the insulin.

**Humulin R® U-500** insulin is for subcutaneous injection only. **Humulin R® U500** insulin can also safely be administered subcutaneously using an insulin infusion pump if required. It should not be used intravenously or intramuscularly.

**Humulin R® U500** insulin will be commenced by the national severe insulin resistance clinic at Addenbrooke's Hospital. The clinic will provide the prescriptions for the first three months and the GP will provide prescriptions thereafter. The starting dose and frequency of doses will be decided on the basis of the doses of regular insulin (100 units per ml) already being taken by the patient. The doses will be titrated according to the regular blood glucose monitoring performed by the patient and by the presence/absence of hypoglycaemia. The patient will be stabilized on **Humulin R® U500** insulin by the national severe insulin resistance team. The national severe insulin resistance team will be available to support the GP if any problems arise or if advice is needed.

The patient will be given education regarding the safe storage and administration of the insulin by the national severe insulin resistance team.

The patient will be issued with a treatment card with details of their insulin and doses and instructions to be followed in case of illness, emergency, hypoglycaemia or hospital admission.

# 7 Adverse effects

## 7.1 Hypoglycaemia

As with all insulins, the most frequent adverse event is hypoglycaemia. Severe hypoglycaemia may develop 18 to 24 hours after the original injection of **Humulin R® U500** insulin. Hypoglycaemia when using **Humulin R® U500** can be prolonged and severe.

Symptoms of mild to moderate hypoglycaemia may occur suddenly and can include:

- Sweating
- Drowsiness
- Dizziness
- sleep disturbances
- palpitations
- anxiety
- tremor
- blurred vision
- hunger
- slurred speech
- restlessness
- depressed mood
- tingling in the hands, feet, lips, or tongue
- irritability
- light headedness
- abnormal behaviour
- inability to concentrate
- unsteady movement
- headache
- personality changes

Signs of severe hypoglycaemia can include:

- disorientation
- seizures
- unconsciousness
- coma
- death

Early warning symptoms of hypoglycaemia may be different or less pronounced under certain conditions, such as long duration of diabetes, autonomic diabetic neuropathy, use of medications such as beta blockers,

changing insulin preparations, or intensified control of diabetes. Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycaemia. Patients who experience hypoglycaemia without early warning symptoms should monitor their blood glucose more frequently, especially prior to activities such as driving.

Mild to moderate hypoglycaemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as fruit juice, non-diet carbohydrate-containing drinks or glucose tablets.

**The patient will receive education by the national severe insulin resistance clinic team regarding safe detection and management of hypoglycaemia.**

## 7.2 Hypokalaemia

Insulin stimulates potassium movement into the cells, possibly leading to hypokalaemia, which if untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk of hypokalaemia (eg, patients using potassium-lowering medication eg thiazide diuretics).

## 7.3 Injection site problems

Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). This is usually resolved/ avoided by regularly rotating injection sites.

## 7.4 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including **Humulin R® U500** insulin. Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

### 7.4.1 Local allergy

Patients occasionally experience erythema, local oedema, and pruritus at the site of injection. This condition usually is self-limiting. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

### 7.4.2 Systemic allergy

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy (anaphylaxis) may be life threatening.

### 7.5 Weight gain

Weight gain can occur with some insulin therapies and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

### 7.6 Peripheral Oedema

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

### 7.7 Hyperglycaemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome

Hyperglycaemia, diabetic ketoacidosis, or hyperosmolar coma may rarely develop if the patient takes less **Humulin R® U500** insulin than needed to control blood glucose levels. This could be due to increases in insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses or use of drugs that affect glucose metabolism or insulin sensitivity. Early signs of diabetic ketoacidosis include glycosuria and ketonuria. Polydipsia, polyuria, loss of appetite, fatigue, dry skin, abdominal pain, nausea and vomiting and compensatory tachypnoea come on gradually, usually over a period of some hours or days, in conjunction with hyperglycaemia and ketonaemia. Severe sustained hyperglycaemia may result in hyperosmolar coma or death.

### 7.8 Renal or hepatic impairment

Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

See the Summary of Product Characteristics (SPC) for further information on adverse events.

## 8 Cautions and interactions

**Humulin R® U500 insulin contains 500 units of insulin in each millilitre (5-times more concentrated than regular human insulin 100units/ml). For Humulin R® U500 insulin, extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycaemia.**

### 8.1 Preventing dispensing errors

The **Humulin R® U500** insulin vial contains 20 mL, versus regular UK insulin vials, which contains 10 ml. It is marked with a band of diagonal brown stripes. “U500” is also highlighted in red on the label.

### 8.2 Preventing prescribing and administration errors

The prescribed dose of Humulin R® U500 should always be expressed in 'marks' of Humulin R® U500 along with corresponding markings on the syringe the patient is using (eg a 0.5ml or 1ml insulin syringe).

## 9 Contraindications

**Humulin R® U500** insulin is contraindicated during episodes of hypoglycemia and in patients hypersensitive to **Humulin R® U500** or any of its excipients.

## 10 Interactions

### 10.1 Drug interactions

The concurrent use of oral hypoglycaemic diabetes agents with **Humulin R® U500** is not recommended since there are limited data to support such use. A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood-glucose-lowering effect of **Humulin R® U500** insulin and susceptibility to hypoglycaemia:

- Oral hypoglycaemic diabetes agents, salicylates, sulpha antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors [SSRIs]), pramlintide, disopyramide, fibrates, fluoxetine, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (eg octreotide), and alcohol.

### 10.2 Drugs that may reduce the blood-glucose-lowering effect

Corticosteroids, isoniazid, certain lipid-lowering drugs (eg, niacin), oestrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents, somatropin, atypical antipsychotics, glucagon, protease inhibitors and thyroid replacement therapy.

### 10.3 Drugs that may increase or decrease blood-glucose-lowering effect

- Beta blockers, clonidine, lithium salts, and alcohol.
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycaemia.

### 10.4 Drugs that may mask the signs of hypoglycaemia:

- Beta-adrenergic blocker
- Clonidine
- Guanethidine
- reserpine.

## 11 Actions to take in the event of abnormal test results/symptoms

If any unusual or serious adverse effect is reported please contact the national severe insulin resistance team for further advice.

## 12 Contact numbers for advice and support

| Post | Telephone |
|---|---|
| Hospital switchboard | 01223 245151 |
| Consultant | 01223 769305 |
| Consultant | 01223 767923 |
| Locum consultant | 01223769046 |
| Research sister | 01223 336080 |
| Diabetes specialist nurse | 01223 768455 |
| Diabetes specialist nurse | 01223 596096 |

## 13 Monitoring compliance with and the effectiveness of this document

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|---|---|
| **Blood glucose monitoring** | By the patient and reviewed by the severe insulin resistance team and the GP |
| **HbA1c/ blood glucose/ urea and electrolytes (U&E)/eGFR lipid profile/ full blood count (FBC)** | Will be measured by hospital clinic initially – this may pass to the GP but only after consultation between the hospital specialist and the GP |

The national severe insulin resistance team will inform GPs and the patients of the frequency of blood glucose monitoring and HBA1c and other blood testing as required.

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