NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared care guideline

Humulin R® U500 insulin for patients with severe insulin resistance

Executive Summary

- Humulin R U500 insulin is a high strength insulin with 500 units/ml of insulin**.**
- **Humulin R U500 insulin is only available as a Kwikpen device**
- Humulin R® U500 insulin will be commenced by the National Severe Insulin Resistance Clinic at Addenbrooke's Hospital only if a shared care agreement is in place. The clinic will provide the prescriptions for the first three months and the GP will provide prescriptions thereafter.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document

Sharing of care depends on communication between the specialist, GP and the patient or their parent/ carer. 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/ healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here.

1 Scope

For prescribing by general practitioners (GPs).

2 Aim

To provide advice on the safe prescribing Humulin R® U500 insulin (soluble human insulin 500 units/ml) for patients with severe insulin resistance.

3 Introduction

In the UK insulin is usually formulated at a concentration of 100 units per ml, with some higher strengths available. Humulin R® U500 insulin is a concentrated formulation of soluble insulin (500 units per ml) available as a Kwipen device.

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 Abbreviations

- GP general practitioner
- rDNA ribosomal DNA
- HbA1C glycated haemoglobin
- eGFR estimated glomerular filtration rate
- FBC full blood count
- U&Es urea and electrolytes

5 Drug details

5.1 Pharmacology

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.

5.2 Contraindications

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

5.3 Cautions

Humulin R® U500 insulin contains 500 units of insulin in each ml (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.

5.4 Prescribing and administration

Humulin R® U500 insulin will be commenced by the National Severe Insulin Resistance Team at Addenbrooke's Hospital. The patient will be seen in an outpatient clinic. Once a shared care agreement is in place, 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.

Humulin R U500 insulin will be prescribed as a Kwikpen device, this device is calibrated to measure doses of multiples of 5 units and doses should therefore be multiples of 5 units. No calculations are required and the dose to be injected is the dose displayed on the pen.

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.
Humulin R® U500 insulin should not be used intravenously or intramuscularly.

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.

5.5 Dispensing

Humulin R U500 is not licensed in the UK and must be imported from the USA, where it is licensed.

It was historically available as a multidose vial which was accessed using a needle and calibrated insulin syringe.

This has been replaced by a pre-filled pen device (KwikPen®) which allows the intended dose to be dialled up in an identical manner to other insulin pens without needing to use a needle and syringe. Due to the concentration of insulin the dose can only be given in 5 unit increments. These pre-filled KwikPens® are also unlicensed in the UK and are imported from the USA via the same importer as the multidose vials.

All patients previously using the multidose vial will be switched over to the pre-filled KwikPen under the supervision of the NSIR.

The Kwipen is a distinctive turquoise colour clearly marked 500 units/ml. These pens do not require special disposable needles.

6 Adverse effects

6.1 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.

6.2 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 (e.g. patients using potassium-lowering medication e.g. thiazide diuretics).

6.3 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.

6.4 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.

6.4.1 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.

6.4.2 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.

6.5 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.

6.6 Peripheral Oedema

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

6.7 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.

6.8 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.

7 Drug Interactions

7.1 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 (e.g. octreotide), and alcohol.

Drugs that may reduce the blood-glucose-lowering effect
Corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), oestrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents, somatropin, atypical antipsychotics, glucagon, protease inhibitors and thyroid replacement therapy.

Drugs that may increase or decrease blood-glucose-lowering effect
Beta blockers, clonidine, lithium salts, and alcohol.
Pentamidine may cause hypoglycaemia, which may sometimes be followed by yperglycaemia.

Drugs that may mask the signs of hypoglycaemia:
Beta-adrenergic blocker
Clonidine
Guanethidine
Reserpine.

7 Monitoring standards and actions to take in the event of abnormal test results/ symptoms

Test	Standard
Blood glucose monitoring	Initial monitoring by the National Severe Resistance Team and regular monitoring at review. Monitoring by patient and GP
HbA1c **Blood glucose** **U+Es** **eGFR** **Lipid profile** **Full Blood Count**	Initial monitoring by the National Severe Resistance Team and regular monitoring at review. May pass to GP but only after consultation between the hospital specialist and GP.

If any unusual or serious adverse effect is reported please contact the National Severe Insulin Resistance Team for further advice.

Contact numbers at Addenbrooke's Hospital for advice and support

Email: insulinresistanceservice@addenbrookes.nhs.uk

Person/department	Contact number
Hospital Switchboard	**01223 245151**
Consultant (Dr Anna Stears)	**01223 254678**
Diabetes Specialist Nurse	01223 768625 or 01223 348790
Administrator	01223 768455

8 Shared care responsibilities

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.

8.1 Consultant

The decision to start **Humulin R® U500** insulin will be made by a consultant physician at the National Severe Insulin Resistance Team 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:

- Prescribe Humulin R® U-500 insulin for the first 3 months as a Kwikpen device.

- 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. Patients will be instructed to administer doses from the Kwikpen only in multiples of 5 units.

- 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.
- 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® U500** 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.

8.2 Hospital pharmacy

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

8.3 General practitioner

- Monitor patient's overall health and wellbeing.
- Prescribe on-going Humulin R® U500 Kwikpen insulin after the first 3 months.
- Prescribe glucose monitoring strips as required.
- Report any adverse events to the hospital specialist, where appropriate.

8.4 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.

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

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Document management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics http://www.medicines.org.uk/emc