Humulin R® U500 insulin for Patients with Severe Insulin Resistance

Prescribing Support Document

What is Humulin R® U500 insulin and when is it used?

Humulin R® U500 insulin is a concentrated (high-strength) formulation of soluble insulin at 500 units/ml. Humulin R® U500 insulin is not licensed in the UK and must be imported from the USA, where it is licensed. It is available as a KwikPen device. Most commonly used insulin formulations are at a concentration of 100 units/ml. Concentrated insulin formulations are used when patients require very high insulin doses.

The National Severe Insulin Resistance/Lipodystrophy Service at Cambridge University Hospital is a highly specialised NHS service funded directly by NHSE for adults and children with syndromes of severe insulin resistance which are not secondary to obesity. Individuals with severe insulin resistance often require more than 200 units and rarely up to many thousands of units of insulin per day. If 100units/ml insulin formulations are used several injections are required for each insulin dose as the maximum insulin 100units/ml dose that can be injected in one injection is about 50 units. Larger volumes injected subcutaneously may affect the pharmacokinetics of the insulin. Large injection volumes and multiple injections can cause discomfort and lead to poor compliance and poor glycaemic control. Humulin R® U500 insulin is therefore an option 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.

Humulin R® U500 insulin is a polypeptide hormone structurally identical to human insulin synthesised through rDNA technology in a laboratory strain of *Escherichia coli* bacteria. Humulin R® U500 insulin is not modified by any agent that alters its duration of action. Clinical experience has shown that this insulin 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.

NHSE has mandated that Humulin R® U500 insulin can only be commenced by the National Severe Insulin Resistance Clinic if the patient's GP agrees to provide ongoing prescriptions after the clinic provides prescriptions for the first three months.

Please refer to the Cambridgeshire and Peterborough system-wide formulary for links to local and national guidance.

Ⓡ **Restricted,** NO SCG Primary Care may continue therapy following specialist initiation.
Ⓤ **CUHFT only** for patients requiring high doses due to Insulin resistance. Prescribe by brand.

Licensed indications and prescribing good practice

Which health professional will prescribe?

The decision to start a patient who is attending the National Severe Insulin Resistance/Lipodystrophy Service on Humulin R® U500 insulin will be made by a Consultant Physician in the National Severe Insulin Resistance Team at Cambridge University Hospital. Once an agreement is in place with the GP to provide ongoing prescriptions, the clinic will provide the prescriptions for the first three months as a KwikPen device through the hospital outpatient pharmacy and the GP will provide prescriptions thereafter. 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 patient will be stabilised 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 and written information regarding safe administration, dosing schedule and safe storage of Humulin R® U500 insulin by the National Severe Insulin Resistance Team, and will be given guidance on appropriate blood glucose monitoring. Patients will be instructed to administer doses from the KwikPen only in multiples of five units.

Preparations and Dosage

Preparation

Humulin R® U500 insulin will be prescribed as a KwikPen device, which is calibrated to measure doses of multiples of five units and doses should therefore be in five-unit increments. No calculations are required and the dose to be injected is the dose displayed on the pen. The pre-filled KwikPen device allows the intended dose to be dialed up in an identical manner to other insulin pens.

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The KwikPen is a distinctive turquoise colour clearly marked 500 units/ml. These pens do not require special disposable needles and can be used with normal pen needles such as *BD Micro-Fine +*.

Excipients

Glycerin, metacresol, zinc oxide, water for injection, sodium hydroxide and hydrochloric acid.

Dosage and Administration

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.

Contraindications and precautions for use

Contraindications

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

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

Special warnings and precautions for use

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.

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 hyperglycaemia.

Drugs that may mask the signs of hypoglycaemia:

Beta-adrenergic blocker
Clonidine
Guanethidine
Reserpine

Adverse effects

Undesirable effects

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.

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 e.g., thiazide diuretics).

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.

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.

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.

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.

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. Peripheral Oedema

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

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

8. Renal or hepatic impairment

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

Reporting of suspected adverse reactions

Humulin R® U500 is an unlicensed medication in the UK and is imported from the USA. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

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

Test	**Monitoring details**
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.

Specialist clinician responsibility

- Prescribe Humulin R® U-500 insulin for the first three 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.

Primary care clinician responsibility

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

Patient responsibility

- 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.

Contact numbers at Cambridge University Hospital for advice and support

Email: add-tr.insulinresistance@nhs.net

Person/department	Contact number
Hospital switchboard	01223 805000
NSIR Service Administrator	01223 348123
Diabetes specialist nurse	01223 348790

References

1. NHS England. National Programmes of Care and Clinical Reference Groups. NHS Standard Contract for Insulin-Resistant Diabetes Services (All Ages). Published 2013. Accessed 8/11/2024.

2. Food and Drug Administration (FDA). Access Data – Humulin R® U500 prescribing information. Last revised 05/2018. Accessed 8/11/2024.

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