Human U-500 insulin 2018

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Learning Objectives

- Participants will be able to identify when it is appropriate to use U500 insulin
- Participants will be able to state how to determine a starting dose of U500 insulin
- Participants will be able to list 2 situations when it is appropriate to adjust U500 insulin

Complete presentation

Humulin® R U-500:
Insulin monotherapy for patients with type 2 diabetes and uncontrolled blood glucose

*high-dose: >200 units of insulin/day

Humulin® R U-500 Indication and Important Safety Information

Indication

Humulin® R U-500 is a concentrated human insulin indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day.

Limitation of Use: The safety and efficacy of Humulin® R U-500 used in combination with other insulins has not been determined. The safety and efficacy of Humulin® R U-500 delivered by continuous subcutaneous infusion has not been determined.

Important Safety Information for Humulin® R U-500

- Contraindications

  Humulin® R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin® R U-500 or any of its excipients.
- Warnings and Precautions

  Dosing Errors: **Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.**

  Hyperglycemia, Hypoglycemia or Death due to Dosing Errors in the Vial Presentation: Medication errors associated with the Humulin R U-500 vial resulting in patients experiencing hyperglycemia, hypoglycemia, or death have been reported.

Program overview

Rethinking the Appropriate Patient for U-500
Treating patients with type 2 diabetes who require high doses* of insulin

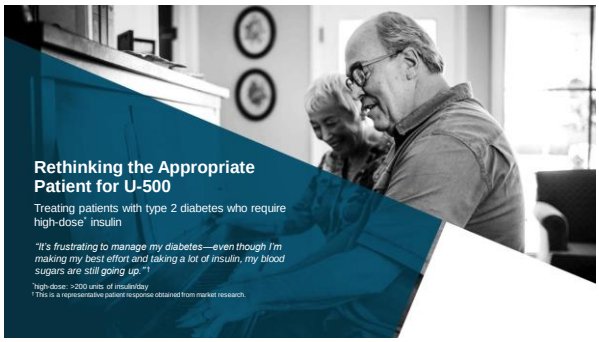
Myths and Facts
Clinical considerations for U-500

Case Study
Envisioning a patient you might see in your practice

Integrating the Humulin® R U-500 KwikPen into Your Practice
Helping you and your patients feel confident

Prescribing and beyond
Resources for healthcare providers and patients

*high doses: >200 units of insulin/day



Rethinking the Appropriate Patient for U-500

Treating patients with type 2 diabetes who require high-dose* insulin

"It's frustrating to manage my diabetes—even though I'm making my best effort and taking a lot of insulin, my blood sugars are still going up."†

*high-dose: >200 units of insulin/day
†This is a representative patient response obtained from market research.

Rethinking U-500

Typical patient you might consider for U-500

- A1C = 9.8% and rising
- TDD of 400 units/day
  - 100/100 units of basal insulin
  - 65/65/70 units of bolus insulin

Would you consider this patient too? What factors influence your decision when considering this patient?

- A1C = 8.2% and stable for 6 months
- TDD of 210 units/day
  - 60/45 units of basal insulin
  - 30/30/45 units of bolus insulin

Myths & Facts

Clinical Considerations for U-500

Myth #1

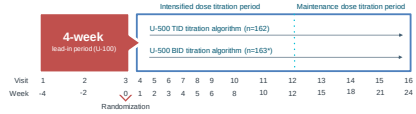
"It seems like U-500 has only been reserved for patients with the highest of insulin requirements."*

I must reserve Humulin® R U-500 for patients requiring more than 300 units of insulin per day.

*This is a representative healthcare provider response obtained from market research.

U-500 Initiation Trial design[1]

- A 24-week, open-label, randomized trial conducted in the United States and Puerto Rico
- Compared 2 treatment regimens—TID vs BID—for U-500 insulin monotherapy replacement of high-dose U-100 insulin
- This trial included a 4-week lead-in period followed by a 24-week treatment period



Select Important Safety Information: Dispensing

- Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct brand and concentration.
- For the Humulin R U-500 vial, particular attention should be paid to the 20-mL vial size, prominent "U-500" and warning statements on the vial label, and distinctive coloring on the vial and carton.

*2 patients who did not receive study drug after randomization were excluded from the analysis.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. **Erratum**, 2016;22(7):905.

Fact #1:

Indication

Humulin® R U-500 is a concentrated human insulin indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day.

Select Important Safety Information: Prescribing

- Dosing errors have occurred when Humulin R U-500 was administered with syringes other than a U-500 insulin syringe. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The dose of Humulin R U-500 should always be expressed in units of insulin.

Patient baseline clinical characteristics[1]	Overall (N=325)
Baseline HbA1c, %	8.7 ± 1.0
HbA1c ≥8.0%, n (%)	234 (72.0)
Diabetes duration, years	15.2 ± 7.4
TDD	
U-100 insulin units at randomization	287.5 ± 80.5
Units/kg	2.4 ± 0.8
No. of injections	
Mean	4.8 ± 1.3
Median (min, max)	5 (2,10)
Type of U-100 insulin at entry, n (%)	
Basal-bolus therapy	
Analog insulin	218 (67.1)
Human insulin	8 (2.5)
Premixed insulin	40 (12.3)
Basal only	20 (6.2)
Other	39 (12.0)

There were no significant differences in baseline demographics and clinical characteristics between the TID and BID treatment groups.

HbA1c=glycated hemoglobin. TDD=total daily dose.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

Approximately 70% of patients were on a total daily dose of 201-300 units of insulin at the start of the U-500 Initiation Trial.[1]

- The Humulin R U-500 study was a 24-week, phase 4, prospective, randomized study conducted in the US and Puerto Rico in patients with T2D and severe insulin resistance (treatment with 201 to 600 units/day U-100 insulin with or without concomitant OADs).
- The trial included a 4-week lead-in period followed by a 12-week intensive dose titration period and subsequent 12-week maintenance phase using R U-500 either TID or BID 30 minutes before meals and dosing titration algorithms based on 4-times daily self-monitored plasma glucose (SMPG) values. Initial dosing proportions were 40:30:30 (breakfast:lunch:dinner) and 60:40 (breakfast:dinner) for the TID and BID regimens respectively.

Select Important Safety Information: Administration

- Instruct patients to always check the insulin label before each injection.
- Use only a U-500 insulin syringe with Humulin R U-500 to avoid administration errors. Do not use any other type of syringe to administer Humulin R U-500. Adhere to administration instructions.
- Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.

1. Wysham C, et al. *Endocr Pract*. 2016;22(6):653-665.

Myth #2

"Although prescribing a lower volume of insulin is an attractive option, I want to make sure it is safe for my patients."*

Patients taking >200 units of insulin per day cannot achieve lower A1C levels.

*This is a representative healthcare provider response obtained from market research.

Fact #2:
U-500 reduced A1C for patients uncontrolled on high-dose U-100 insulins[1]

Average A1C reduction of 1.1% (TID) and 1.2% (BID) at endpoint (24 weeks)†‡

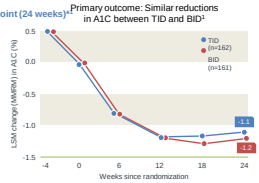
- Mean A1C at baseline for both groups was 8.7%
- Mean A1C at endpoint was 7.5% for TID and 7.4% for BID

The difference in LSM A1C change from baseline between treatment groups (BID vs TID) was -0.10%. The 95% CI (-0.33% to 0.12%) fell within the range established by the noninferiority margin (0.4%), demonstrating clinical equivalence of the 2 treatment regimens.

Select Important Safety Information: If using the Humulin R U-500 KwikPen, patients should be counseled to dial and dose the prescribed number of units of insulin (NO dose conversion is required).

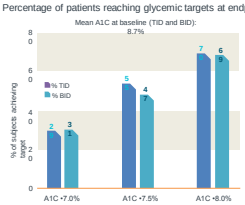
†All efficacy analyses were conducted using the full analysis set defined as all randomized patients receiving at least one dose of study drug at baseline.
LSM=least squares mean. CI=confidence interval. MMRM=mixed model repeated measures.
1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

Primary outcome: Similar reductions in A1C between TID and BID[1]



U-500 helped most patients reach glycemic targets

Percentage of patients reaching glycemic targets at endpoint*[1]



*At 24 weeks for those not at target at randomization. Patients at target (%) at baseline: 1.9% (<7.0%), 9.9% (<7.5%), and 24.8% (<8.0%).

After 24 weeks* using Humulin® R U-500

~70% of patients reached A1C <8.0%
~50% of patients reached A1C <7.5%

NOTE: There was no statistically significant difference in percent-to-target results achieved between TID and BID dosing. All efficacy analyses were conducted using the full analysis set defined as all randomized patients receiving at least one dose of study drug at baseline.

Select Important Safety Information:

- DO NOT transfer Humulin R U-500 from the Humulin R U-500 KwikPen into any syringe for administration. Overdose and severe hypoglycemia can occur
- **Never Share a KwikPen or U-500 Syringe Between Patients,** even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

Myth #3

"Dosing insulin more frequently tends to yield significantly greater A1C reductions for my patients"*

U-500 is more effective at reducing A1C when given TID versus BID.

*This is a representative healthcare provider response obtained from market research.

Fact #3:
TID and BID dosing comparability and clinical equivalence

- No statistically significant difference in A1C reduction* achieved at endpoint between dosing options

Trial results TID and BID[1]

	TID (n=162)	BID (n=161)
Mean baseline A1C (%)	8.7	8.7
Endpoint A1C (%)	7.53	7.41
Overall A1C change from baseline (%)	-1.12 (*P*<0.001)	-1.22 (*P*<0.001)
Reduction in mean daily injections	2 (*P*<0.001)	3 (*P*<0.001)
Mean total daily dose at endpoint (units)	343.1	335
Weight change from baseline (kg)	+5.4	+4.9

Select Important Safety Information: Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen: Changes in insulin, manufacturer, type, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased

*The difference in LSM A1C change from baseline between treatment groups (BID vs TID) was -0.10%. The 95% CI (-0.33% to 0.12%) fell within the range established by the noninferiority margin (0.4%), demonstrating clinical equivalence of the 2 treatment regimens.

1. Hood RC, et al. *Endocr. Rev.* 2015;36(2)(suppl). **Erratum**, 2016;22(7):905

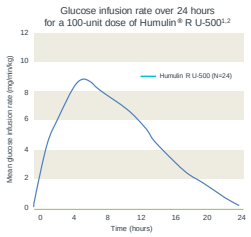
Myth #4

"My patients often complain about the high number of injections they require each day."*

Humulin® R U-500 cannot effectively be used as insulin monotherapy.

*This is a representative healthcare provider response obtained from market research.

Fact #4: Humulin® R U-500 provides both prandial and basal characteristics



Because it has both basal and prandial characteristics, it can be prescribed as insulin monotherapy, usually with 2 or 3 injections.[1]

Starts working within 30 minutes and lasts up to 24 hours*

Select Important Safety Information: Hypoglycemia: Hypoglycemia is the most common adverse reaction associated with insulin, including Humulin R U-500. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Severe hypoglycemia may develop as long as 18 to 24 hours after an injection of Humulin R U-500. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important, such as driving or operating other machinery.

*The time-course action of any insulin may vary in different individuals or at different times in the same individual.

1. Humulin R U-500 [Information for the Physician]. 2015.
2. de la Peña A, et al. *Diabetes Care*. 2011;34(12):2496-2501.

In the U-500 Initiation Trial, all patients were uncontrolled on high-dose insulin therapy, including 69.6% who were on basal-bolus therapy, when they transitioned to U-500 insulin monotherapy.[1]

Basal-Bolus → U-500 Monotherapy

- The Humulin ® R U-500 study was a 24-week, phase 4, prospective, randomized study conducted in the US and Puerto Rico in patients with T2D and severe insulin resistance (treatment with 201 to 600 units/day U-100 insulin with or without concomitant OADs).
- The trial included a 4-week lead-in period followed by a 12-week intensive dose titration period and subsequent 12-week maintenance phase using R U-500 either TID or BID 30 minutes before meals and dosing titration algorithms based on 4-times-daily self-monitored plasma glucose (SMPG) values. Initial dosing proportions were 40:30:30 (breakfast:lunch:dinner) and 60:40 (breakfast:dinner) for the TID and BID regimens, respectively.

Select Important Safety Information:
Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual.

1. Wysham C, et al. *Endocr. Pract.* 2016;22(6):653-665.

Myth #5

Although prescribing a lower volume of insulin is an attractive option, I want to make sure it is safe for my patients.*+

My patients cannot safely take a concentrated insulin like U-500.

*This is a representative healthcare provider response obtained from market research.

Fact #5:
Hypoglycemia incidence and rates: Severe*[1]

Incidence and rates of hypoglycemia in the Humulin® R U-500 Initiation Trial[1]

	TID (n=162)	BID (n=161)
Severe hypoglycemia		
Incidence, n (%)	**3 (1.9)**	**6 (3.7)**
30-day event rate†	0.004 ± 0.028	0.009 ± 0.053

During this trial, hypoglycemia was categorized as documented symptomatic, nocturnal, or severe hypoglycemia. By definition, severe hypoglycemia required assistance from another person for treatment and was accompanied by neurologic/cognitive impairment. Incidence is reported as the number of patients with at least one hypoglycemic episode.

Select Important Safety Information: Early warning symptoms of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system, or in patients who experience recurrent hypoglycemia.

*All hypoglycemia analyses were performed using the full analysis set defined as all randomized patients receiving at least one dose of study drug.
†Events/patients/30 days. Rates are geometric LSM ± SD (severe).
SD=standard deviation.
1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum. 2016;22(7):905

Hypoglycemia incidence and rates: Non-severe[1]

	TID (n=162)	BID (n=161)
Documented symptomatic ≤70 mg/dL		
Incidence, n (%)	149 (92.0)	145 (90.1)
30-day event rate*	3.46 ± 0.33	4.30 ± 0.40
Documented symptomatic <50 mg/dL		
Incidence, n (%)	91 (56.2)	103 (64.0)
30-day event rate*	0.44 ± 0.07	0.54 ± 0.09

	TID (n=162)	BID (n=161)
Nocturnal ≤70 mg/dL		
Incidence, n (%)	126 (77.8)	130 (80.8)
30-day event rate*	0.92 ± 0.11	1.20 ± 0.13
Nocturnal <50 mg/dL		
Incidence, n (%)	59 (36.4)	79 (49.1)
30-day event rate*	0.17 ± 0.03	0.20 ± 0.04

During this trial, hypoglycemia was categorized as documented symptomatic, nocturnal, or severe hypoglycemia. Documented symptomatic hypoglycemia was defined as signs or symptoms associated with hypoglycemia and a plasma glucose ≤70 mg/dL or <50 mg/dL. Nocturnal hypoglycemia was defined as documented symptomatic hypoglycemia occurring between bedtime and waking. Incidence is reported as the number of patients with at least one hypoglycemic episode. All hypoglycemia analyses were performed using the full analysis set defined as all randomized patients receiving at least one dose of study drug.

Select Important Safety Information:
The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of Humulin R U-500 may vary in different individuals or at different times in the same individual and depends on many conditions.

*Events/patients/30 days. Rates are geometric LSM ± SE (documented symptomatic and nocturnal). SE=standard error.
1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum. 2016;22(7):905

The Humulin® R U-500 KwikPen®

No dose conversion needed with U-500 KwikPen
- The Humulin R U-500 KwikPen dials and doses the insulin units prescribed
- If a patient needs a dose of 100 units, they dial to 100 units on the U-500 KwikPen

Designed specifically for high-dose insulin needs[1]
- Delivers up to 300 units in a single injection
- 1500 units contained in each U-500 KwikPen

How it's different from other pens[2]
- The aqua pen body makes the Humulin R U-500 KwikPen stand out from other insulin pens to reduce the potential for confusion[2]
- It's the only pen that dials in 5-unit increments[3]

Select Important Safety Information: DO NOT perform dose conversion when using the Humulin R U-500 KwikPen. The dose window of the KwikPen shows the number of units of Humulin R U-500 to be injected and NO dose conversion is required.
1. Data on file, Lilly USA, LLC. HM20151210a. 2. Data on file, Lilly USA, LLC. HM20151210e. 3. Data on file, Lilly USA, LLC. HM20151210d.

No dose conversion with Humulin® R U-500

Dial or draw to the number of insulin units prescribed. No dose conversion needed.*

Two ways to take U-500 insulin: U-500 KwikPen® or BD™ U-500 Insulin Syringe:

CURRENT

CURRENTLY:
When the U-500 KwikPen or the U-500 syringe is used, no dose conversion is needed—a unit is a unit.

Humulin R U-500 KwikPen (dialed to 100 units)

U-500 insulin syringe (drawn to 100 units)

OUTDATED CONVERSION DO NOT PRESCRIBE U-500 OR VOLUMETRIC SYRINGE OR INSTRUCT HOW TO USE WITH U-500 INSULIN

PREVIOUSLY:
When the U-500 vial was prescribed, the dose had to be converted for a U-100 insulin syringe or a volumetric syringe.

U-100 insulin syringe (drawn to 20 unit mark)

Volumetric syringe (drawn to 0.2 mL mark)

Select Important Safety Information: Humulin R-U500 is available as a KwikPen or a multiple dose vial. Patients using the vial must be prescribed the U-500 insulin syringe to avoid medication errors.

*Both the Humulin R ® U-500 KwikPen and the BD U-500 insulin syringe dose the insulin units prescribed. Dose conversion is no longer needed when using this syringe with Humulin ® R U-500 vials. Only the U-500 insulin syringe should be prescribed and used with the U-500 vial to help reduce medication errors.

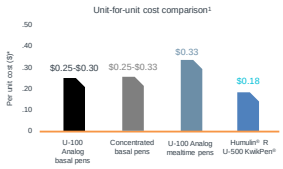
Myth #6

On a per unit of insulin basis, U-500 costs more than analog insulins.

*This is a representative provider response obtained from market research.

Fact #6:
Unit for unit, U-500 KwikPen® is the lowest-priced pen available[1]

- For patients with coinsurance, high deductible health plans, or patients in the Medicare donut hole, the unit cost of insulin is important
- On a per-unit basis, the U-500 KwikPen is the lowest cost insulin pen available for your severely insulin-resistant patients
- Patients transitioning from an analog basal-bolus regimen to U-500 as insulin monotherapy will pay a single cost or copay for their insulin



*Wholesale Acquisition Cost from RED BOOK Online® as of January 10, 2017.

1. RED BOOK Online® as of January 2017.

Select Important Safety Information: Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

Case Study

Envisioning a patient you might see in your practice

*"I have to take a lot of insulin just to stay in control. But sometimes it seems even that's not enough."**

This is a representative patient response obtained from market research.

Tony*

Patient Demographics	
Age, years	60
Weight, lbs	230
BMI, kg/m²	35
Baseline HbA1c, %	8.2
Diabetes duration, years	17

HbA1c=glycated hemoglobin
*Hypothetical patient

Current clinical characteristics	
Number of concomitant OADs (Metformin, DPP-4 inhibitor)	2
Amount of U-100 insulin, units	
Basal insulin dose	60/45
Bolus insulin dose	30/30/45
No. of injections	
Basal	2
Bolus	3

How would YOU treat this patient going forward?

- How would you initiate Humulin® R U-500?
- Would you use it as insulin monotherapy?
- Would you prescribe it BID or TID?

Humulin® R U-500 KwikPen into your Practice

Helping you and your patients feel confident

This is a representative patient response obtained from market research.

U-500 Initiation Trial: A clinical framework for initiating patients on Humulin® R U-500

STEP 1: Determine starting dose[1]

Patient A1C ≤8% OR patient's mean SMPG <183 mg/dL within the past 7 days

YES	NO
Start at 80% of final U-100 TDD*	Start at 100% of final U-100 TDD*

STEP 2: Determine dose proportions[1]

TID dose proportions		BID dose proportions	
BEFORE BREAKFAST	40%	BEFORE BREAKFAST	60%
BEFORE LUNCH	30%		
BEFORE DINNER	30%	BEFORE DINNER	40%

Select Important Safety Information: Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-500. If hypersensitivity reactions occur, discontinue Humulin R U-500; treat per standard of care and monitor until symptoms and signs resolve.

*After calculating TDD, round down to the nearest increment of 5.
SMPG=self-monitored plasma glucose.
1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum. 2016;22(7):905

Starting Tony* on a BID or TID regimen

Algorithms for initiating BID or TID doses		
A1C	8.2%	
Mean SMPG[2]	187 mg/dL	
Calculating the starting dose		
Current dose of U-100 insulin (basal and bolus combined)	**210 units**	
A1C %	<8 and ≥7	≤7
Mean SMPG[2]	≥183 mg/dL	≤100% TDD
Starting dose of U-500	**210 units**	
BID/TID	BID (60:40)	TID (40:30:30)
Before breakfast	210 x 0.6=126	210 x 0.4=84
Before lunch		210 x 0.3=63
Before dinner	210 x 0.4=84	210 x 0.3=63
Nearest unit increment[3]	**125:80**	**80:60:60**

*Hypothetical patient.
[2]Mean SMPG in the 7 days before U-500 initiation.
[3]Rounding down to the nearest increment of 5.

How would you titrate U-500?

U-500 Initiation Trial: A clinical framework for titrating patients on Humulin® R U-500

STEP 3: Titration[1]

- Treat-to-target dosing algorithms titrated TID or BID regimens to achieve fasting and pre-meal SMPG 71-130 mg/dL
- Both doses of the BID regimen were titrated; only 2 of 3 TID doses were titrated (those most needing adjustment)
- Dose reductions were prioritized over dose increases for hypoglycemia
- U-500 dosing was recommended 30 minutes before meals
- Patients checked their blood glucose before each meal and at bedtime daily
- Patients also checked their blood glucose at 3 AM if they had increased their dose in the last 48 hours

Select Important Safety Information: Hypokalemia: Insulin use can lead to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

An effective treat-to-target dosing algorithm with 2 injections of U-500 per day[1]

BID initial dose proportions: 60:40[1]

INSULIN DOSE TO ADJUST	PLASMA-EQUIVALENT GLUCOSE VALUE*	SMPG (mg/dL)	DOSE TITRATION†
PRE-BREAKFAST	MEDIAN‡ PRE-DINNER SMPG	≤70§	-10%
		71-130	No change in dose
PRE-DINNER	MEDIAN‡ PRE-BREAKFAST SMPG	131-180	+5%
		181-220	+10%
		>220	+15%

*Patients should check their blood glucose before each meal and at bedtime daily, and at 3 AM if they have increased their dose in the last 48 hours.

†Used conventional rounding to nearest 5-unit increment.

§10% breakfast dose reduction for median pre-lunch or pre-dinner SMPG ≤70 mg/dL. 10% dinner dose reduction for median bedtime or pre-breakfast or single 3 AM SMPG ≤70 mg/dL.

‡Median of 3 most recent daily SMPG readings.

Select Important Safety Information: Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists: Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

An effective treat-to-target dosing algorithm with 3 injections of U-500 per day[1]

TID initial dose proportions: 40:30:30[1]

INSULIN DOSE TO ADJUST	PLASMA-EQUIVALENT GLUCOSE VALUE*	SMPG (mg/dL)	DOSE TITRATION†
PRE-BREAKFAST	MEDIAN‡ PRE-LUNCH SMPG	≤70§	-10%
		71-130	No change in dose
PRE-LUNCH	MEDIAN‡ PRE-DINNER SMPG	131-180	+5%
		181-220	+10%
PRE-DINNER	MEDIAN‡ PRE-BREAKFAST SMPG	>220	+15%

*Patients should check their blood glucose before each meal and at bedtime daily, and at 3 AM if they have increased their dose in the last 48 hours.

†Used conventional rounding to nearest 5-unit increment.

§10% dinner dose reduction for median bedtime or pre-breakfast or single 3 AM SMPG ≤70 mg/dL.

‡Median of 3 most recent daily SMPG readings.

Only 2 of 3 TID doses were titrated (those most needing adjustment)

Select Important Safety Information: Adverse Reactions include hypoglycemia, allergic reactions, lipodystrophy, injection site reactions, weight gain, peripheral edema, and immunogenicity.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905

Prescribing and beyond

*"Sometimes it feels like I can't win—even with lower numbers, I still have a long way to go. I'd welcome anything that could give me better control."**

This is a representative patient response obtained from market research.

Steps for starting Humulin® R U-500 KwikPen®

When starting **new patients** on the U-500 KwikPen, follow these steps:

1. Determine patient's starting dose. You may wish to refer to the U-500 Initiation Trial[1] algorithm.

   Note: Because the U-500 KwikPen delivers units in increments of 5, the starting dose must be a multiple of 5.

2. Show the patient how to dial and dose the units prescribed with the U-500 KwikPen.

   Remember: No dose conversion is required. The U-500 KwikPen dials and doses the units prescribed.

Select Important Safety Information: Prescribe Humulin R U-500 ONLY to patients who require more than 200 units of insulin per day.

1. Hood RC, et al. *Endocrine Practice.* 2015;21(7):782-793. Erratum. 2016;22(7):905.

When prescribing the Humulin® R U-500 KwikPen® for your patients

Be sure to

- Specify the full product name: Humulin R U-500 KwikPen
- Indicate the administration schedule as TID dosing or BID dosing
- Record the required number of units of U-500 insulin per dose and specify before which meals the doses are to be taken to ensure the appropriate supply is dispensed at the pharmacy
- Prescribe pen needles. BD Pen Needles recommended*
- Write "Do Not Substitute" on the prescription

Example prescription: The prescription details should be individualized and determined, by the prescriber, in accordance with the needs of the patient.

Select Important Safety Information: Advise the patient to read the Patient Information and Instructions for Use.

*BD, BD Logo, BD AutoShield Duo, and BD Ultra-Fine are trademarks of Becton, Dickinson and Company.

Important considerations when starting patients on the Humulin® R U-500 KwikPen®

Information to share with your patients

- Explain how many times a day patients should inject and the dose at each injection
- Advise patients to inject U-500 30 minutes before eating a meal to reduce the risk of hypoglycemia
- Demonstrate how to dial the U-500 KwikPen to deliver the insulin dose
- Instruct patients not to withdraw insulin from the U-500 KwikPen using a syringe because overdose and severe hypoglycemia may occur
- Patients should call their pharmacy to check availability; some pharmacies may not stock U-500, but it should be available within 24 to 48 hours
- Tell your patients about the U-500 Savings Card to help eligible patients with the cost of their prescription

Select Important Safety Information: Instruct patients to always check the insulin label before administration to confirm the correct insulin product is being used.

Summary

U-500 may do more than reduce A1C for patients on high doses of insulin

- Effective in patients requiring more than 200 units of insulin per day[1]
- Reduced A1C levels by 1.1% in severely insulin-resistant patients whose glycemic levels were uncontrolled[1]
- Effective as insulin monotherapy with basal and prandial properties[1]
- Improved glycemic control with 2 or 3 daily injections[1]
- Allows patients to pay a single co-pay for their insulin, when U-500 is their only insulin

Select Important Safety Information: Administer Humulin R U-500 subcutaneously two or three times daily approximately 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy.

*All efficacy analyses were conducted using the full analysis set as all randomized patients receiving at least one dose of study drug at baseline.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum. 2016;22(7):905

Additional Important Safety Information

- Drug Interactions: Some medications may alter glucose metabolism and may necessitate insulin dose adjustment. Signs of hypoglycemia may be reduced or absent in patients taking antiadrenergic drugs. Particularly close monitoring may be required.
- Use in Specific Populations

  Pregnancy Category B: While there are no adequate and well-controlled studies in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.

  Pediatric Use: There are no well-controlled studies of use of Humulin R U-500 in children. Standard precautions as applied to use of Humulin R U-500 in adults are appropriate for use in children.

  Geriatric Use: There are no well-controlled studies of use of Humulin R U-500 in geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.

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

Additional Important Safety Information (continued)

- Dosage and Administration

  DO NOT perform dose conversion when using a U-500 insulin syringe. The markings on the syringe show the number of units of Humulin R U-500 to be injected. Each marking represents 5 units of insulin.

  Instruct patients using the vial to use only a U-500 insulin syringe and on how to correctly draw the prescribed dose into the syringe. Confirm that the patient has understood these instructions and can correctly draw the prescribed dose with their syringe.

  Individualize the dose of Humulin R U-500 based on metabolic needs, blood glucose monitoring results, and glycemic control goal.

  Do NOT administer Humulin R U-500 intravenously or intramuscularly.

  Do NOT mix Humulin R U-500 with other insulins.

Additional Important Safety Information (continued)

- Storage

  Protect from heat and light. Do not freeze. Do not use Humulin R U-500 after the expiration date stamped on the label.

  Humulin R U-500 Vials: Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opened (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any opened vial after 40 days of use, even if there is insulin left in the vial.

  Humulin R U-500 KwikPen: Unopened Humulin R U-500 KwikPens should be kept in a refrigerator. Opened (in-use) Humulin R U-500 KwikPens should be kept at room temperature and used within 28 days of opening. Do not refrigerate opened KwikPens. Throw away any opened KwikPen after 28 days of use, even if there is insulin left in the pen.

Humulin® R U-500 is also available in a vial

U-500 Vial Information

Key points when initiating Humulin R U-500 in a vial

- Clearly instruct patients that they are using an insulin that is 5 times more concentrated than U-100 insulin
- Patients should never allow others to use their vial of Humulin R U-500 insulin
- When prescribing Humulin R U-500, include the dose in units, and a separate prescription for the BD™ U-500 insulin syringes
- While the price per vial may be more than U-100 insulin, note that 1 vial of Humulin R U-500 contains the same amount of insulin as 10 vials of U-100

This list is not comprehensive. Individual patient needs should be considered.

Select Important Safety Information: Administration:
- Instruct patients to always check the insulin label before each injection.
- Use only a U-500 insulin syringe with Humulin R U-500 to avoid administration errors. Do not use any other type of syringe to administer Humulin R U-500. Adhere to administration instructions.
- Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.

Steps for starting Humulin® R U-500 in a vial

U-500 Vial Information

Patients new to U-500 vial

1. **Determine patient's starting dose.**
   You may wish to refer to the U-500 Initiation Trial algorithm.[1]

   Note
   Because the U-500 syringe delivers units of insulin in increments of 5, the starting dose must be a multiple of 5.

2. **Show the patient how to draw to the units prescribed with the U-500 syringe.**
   Remember, no dose conversion is required. The U-500 syringe draws to the units prescribed.

NOTE: Patients should use ***only*** the BD™ U-500 insulin syringe to administer Humulin R U-500.

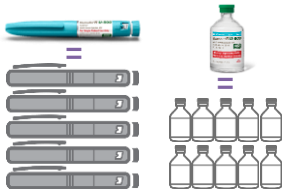
Select Important Safety Information:

- DO NOT perform dose conversion when using a U-500 insulin syringe. The markings on the syringe show the number of units of Humulin R U-500 to be injected. Each marking represents 5 units of insulin.
- Humulin R U-500 is available as a KwikPen or a multiple dose vial. Patients using the vial must be prescribed the U-500 insulin syringe to avoid medication errors.

1. Hood RC, et al. *Endocrine Practice*. 2015;21(7):782-793. Erratum, 2016;22(7):905.

Dispensing U-500

- One Humulin® R U-500 KwikPen® contains 1500 units of insulin per pen—the same amount as 5 U-100 KwikPens.[1]
- The U-500 KwikPen is packaged with 2 pens per pack—3000 units of insulin
- One vial of Humulin R U-500 contains the same amount of insulin as 10 vials of U-100



U-100 U-100

1. Data on file, Lilly USA, LLC. HM20151210d.

Select Important Safety Information: Humulin R U-500 Vials: Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opened (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any opened vial after 40 days of use, even if there is insulin left in the vial.