Are We Really Going to Buy Into

Individualized Dosing?

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One of my patients…

- 45 year-old HIV+ woman
- Long history of medication intolerance
- Started a fos-amprenavir containing regimen (without ritonavir), 2 x 700 mg tablets twice daily (total 2800 mg/day).
  - Daytime fatigue, which she attributed to the morning dose
  - Enquired about taking the entire dose at night, otherwise does not wish to continue.

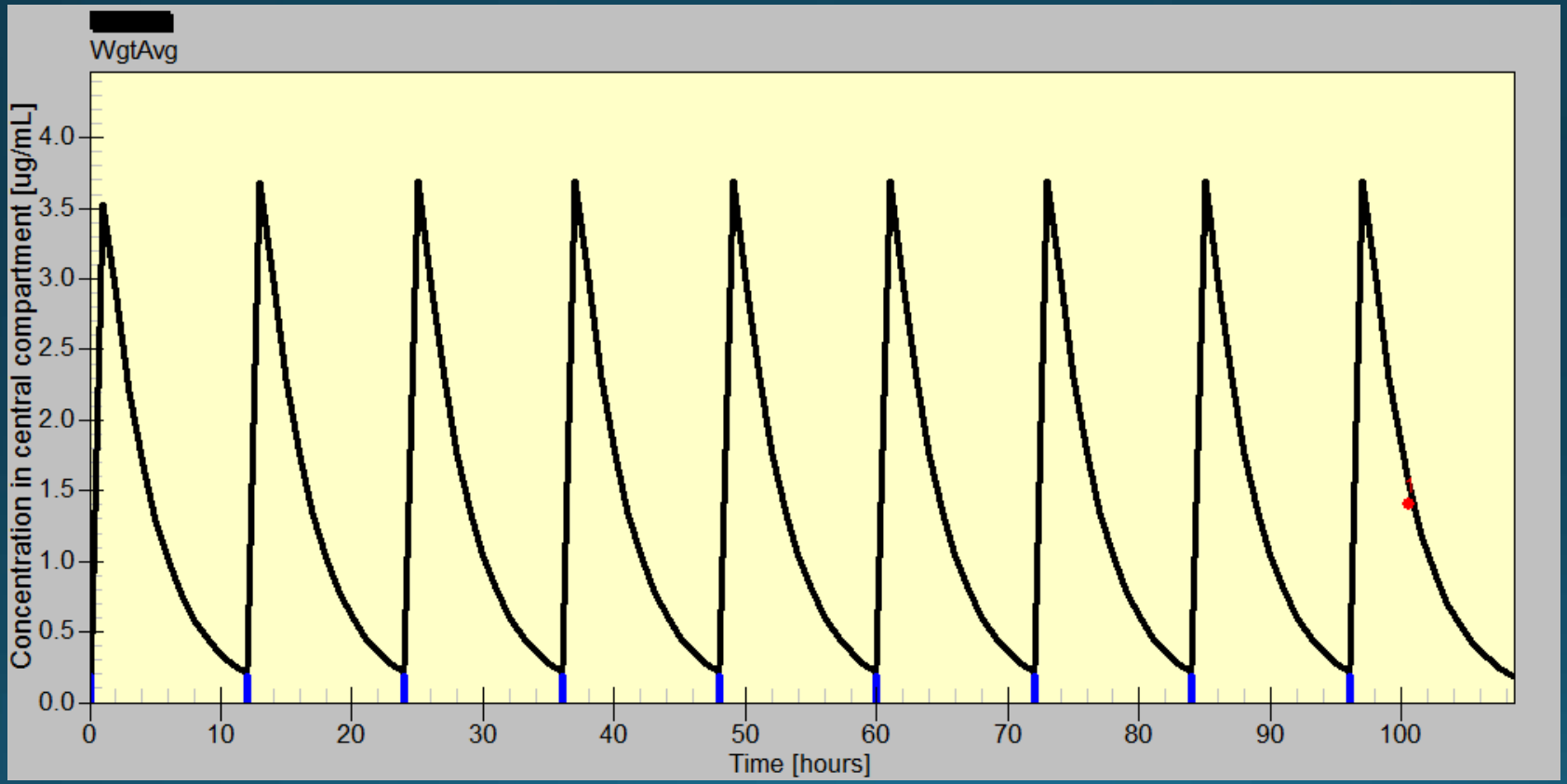
Patient 1 Options

- Tell her the problem is in her head and press on.
- Change to 4 tablets every evening, informing her that you hope it is sufficient to maintain virologic control without new (worse?) side effects.
- Change medications, yet again.
- Measure amprenavir concentration(s) and attempt rational drug management

Patient 1 Data

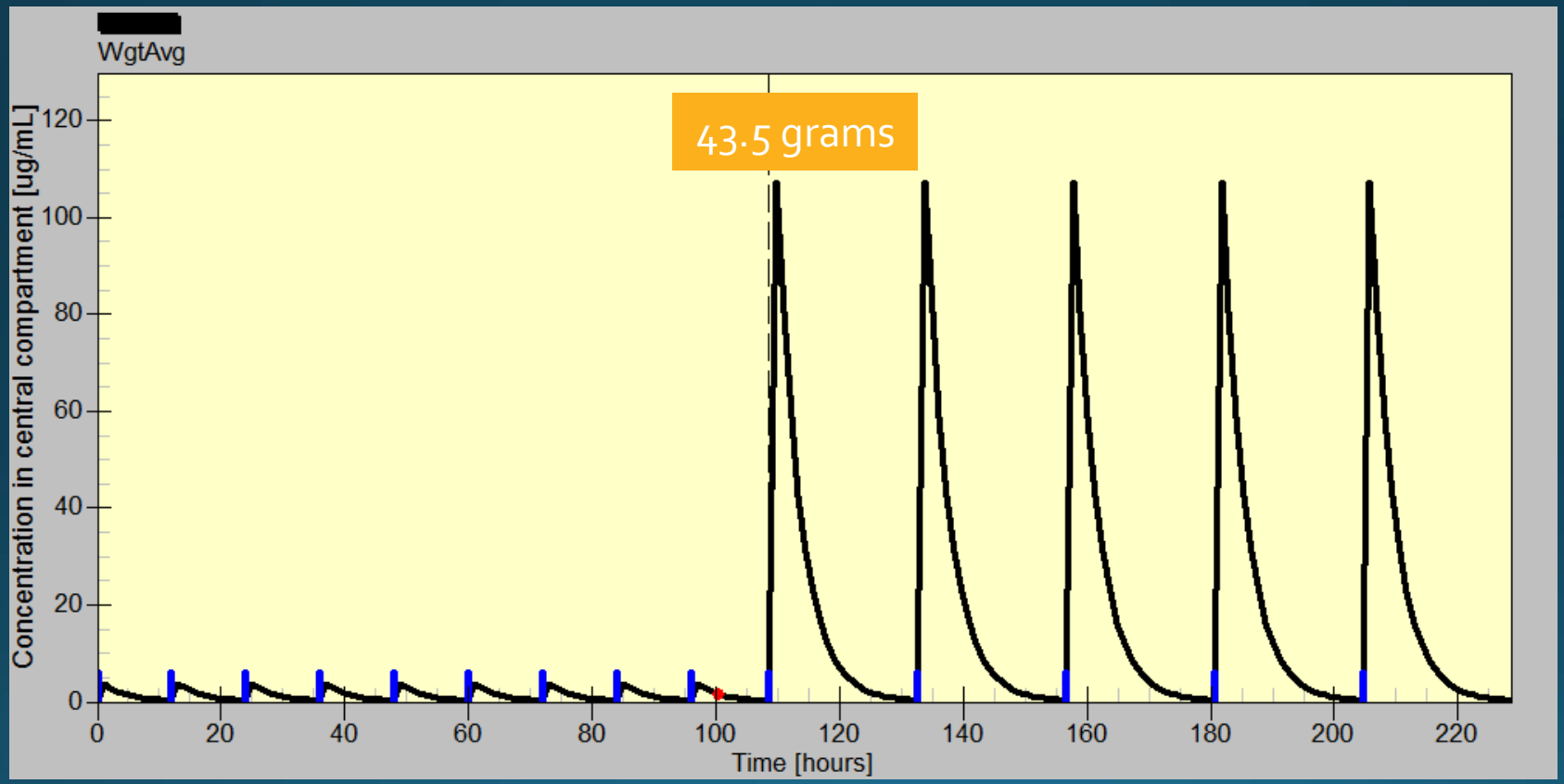
- On the standard dose of 1400 mg bid, a serum amprenavir concentration of 1.4 mg/L was measured 4.5 hours after her previous dose (1 week turn-around time).
- Resistance testing indicated no resistance to amprenavir
- Target amprenavir trough for wild-type virus suggested to be 0.23 to 0.4 mg/L
- Can she take all 4 pills at night???

First fit

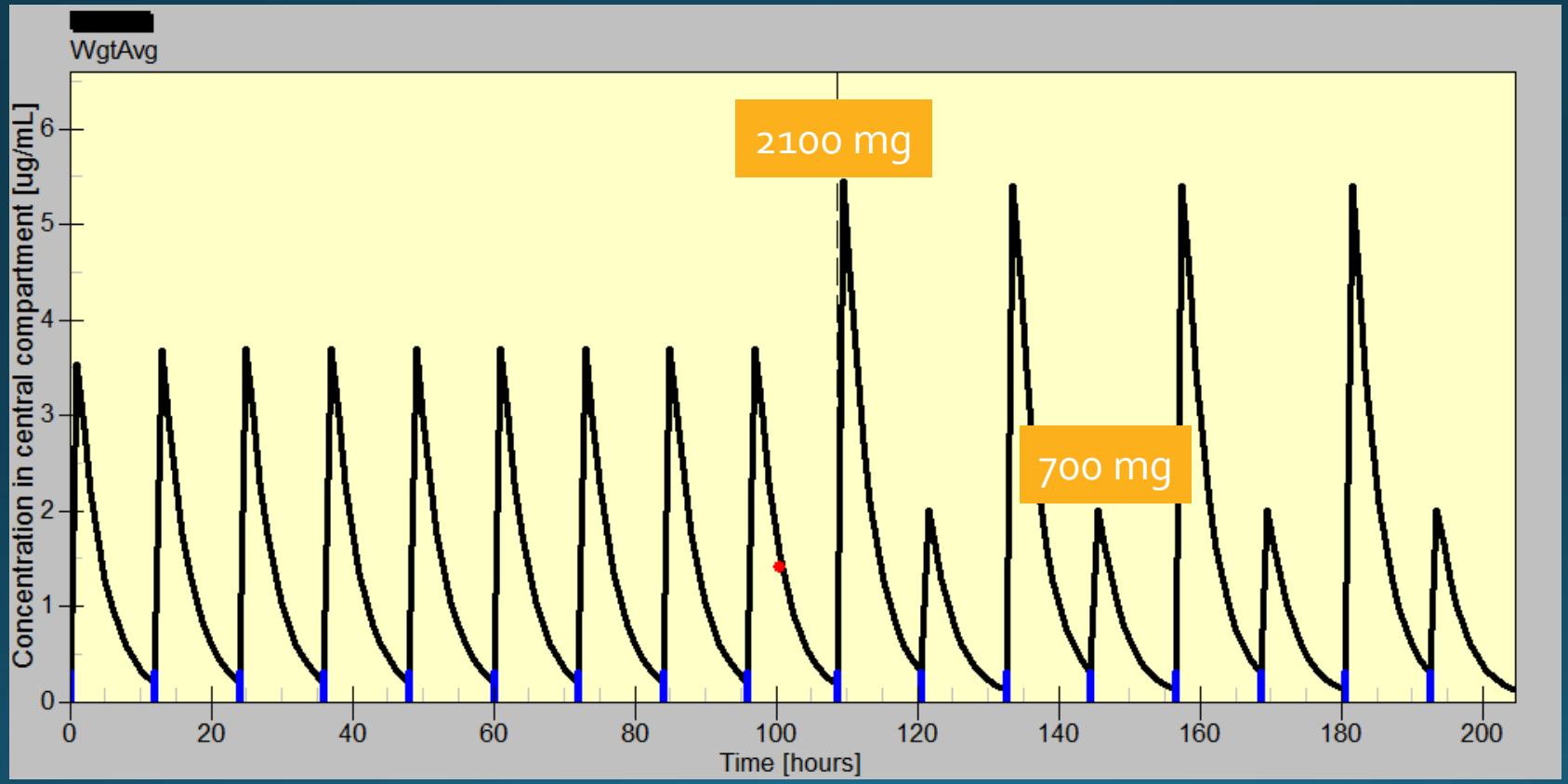


0.27 mg/L

Once daily dosing

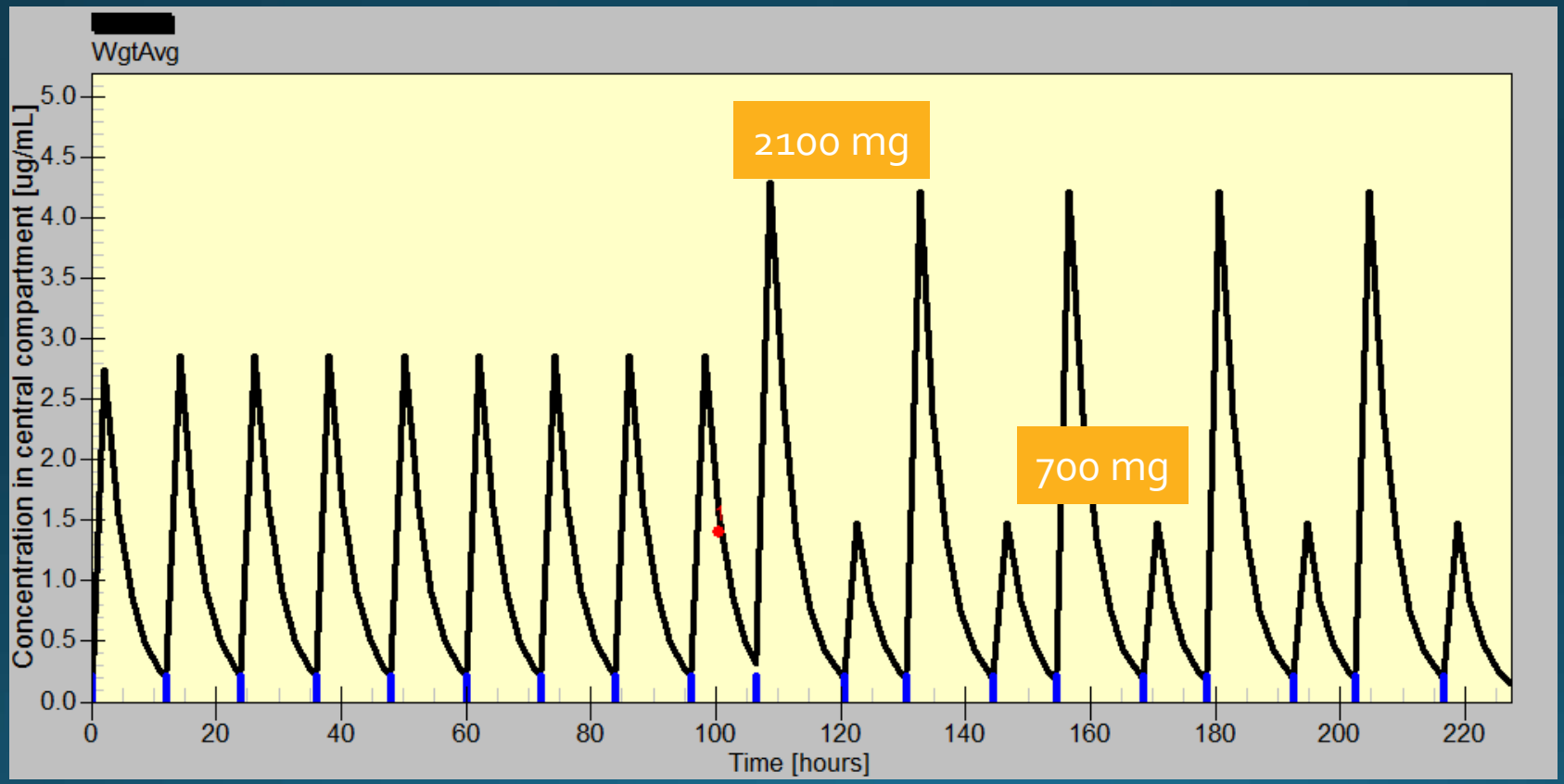


Every 12 h



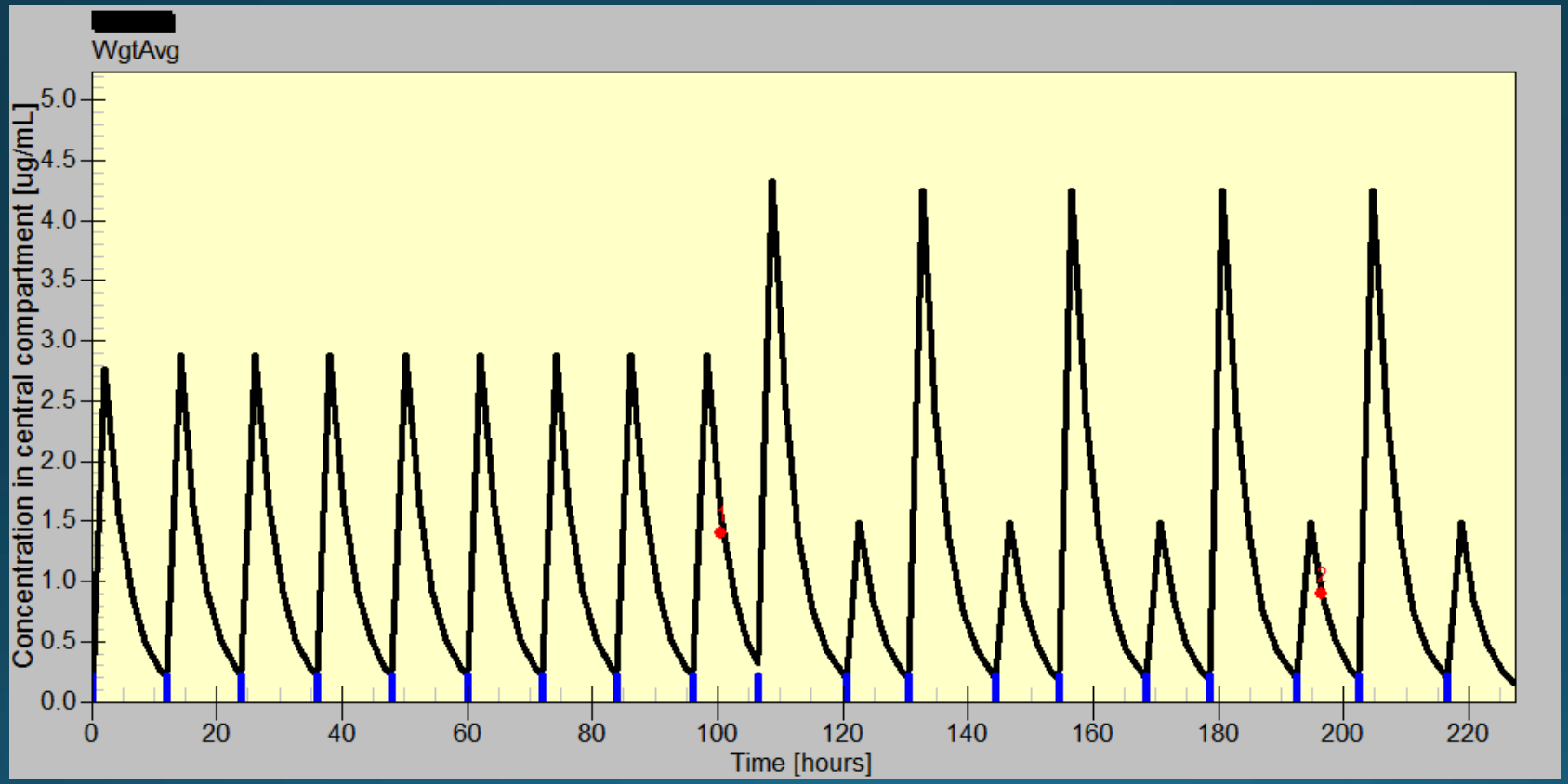
0.11 mg/L

Every 10, 14 h



0.26 mg/L

Results!

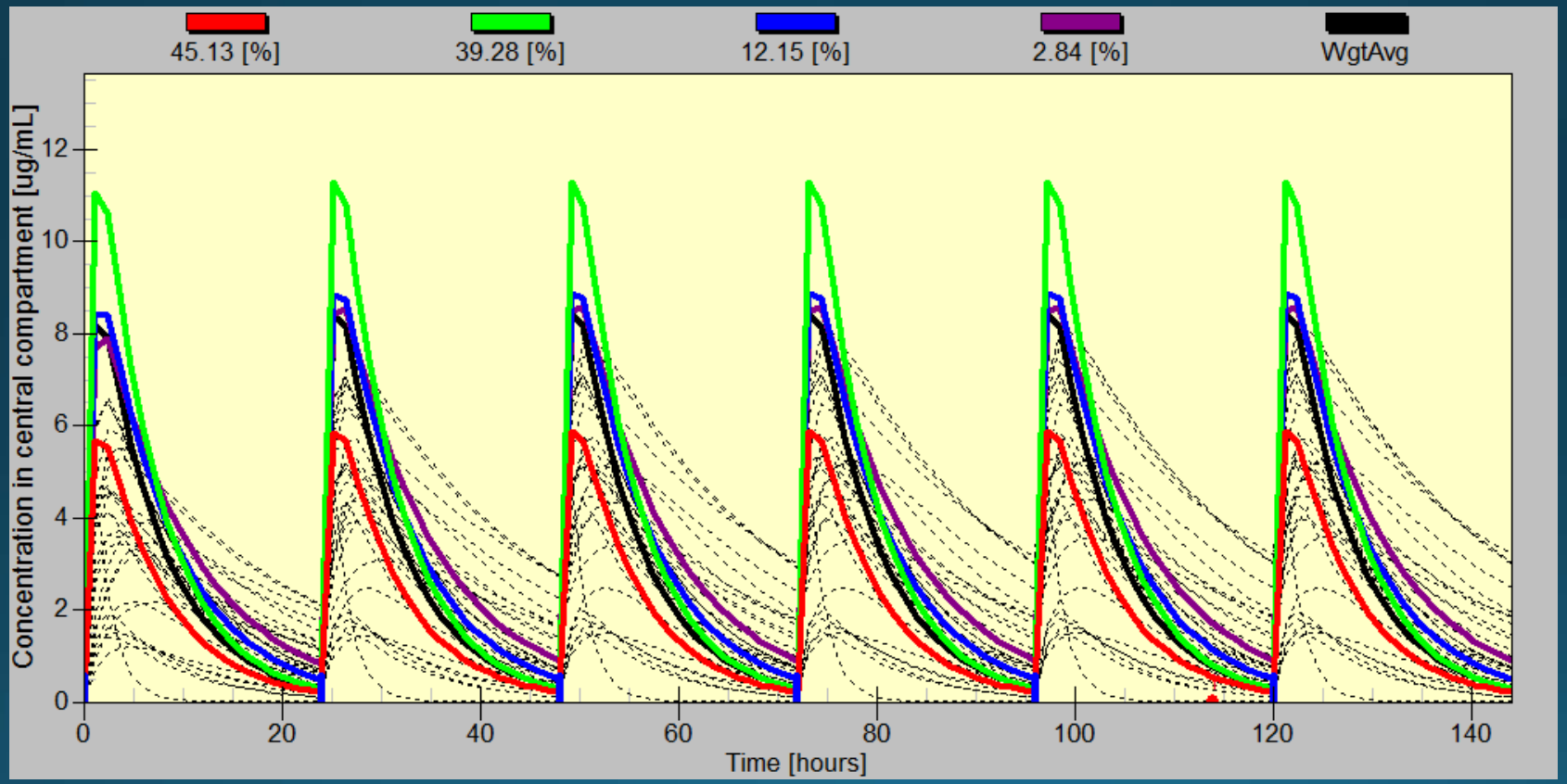


0.26 mg/L

A second patient…

- 18 year old woman, taking atazanavir 400 mg once daily
- Repeatedly swears that she is taking it
- Yet bilirubin is normal, viral load is 30,000 copies/mL, CD4+ cell count is <20 cells/mL
- Level 18 hours after dose is <10 ng/mL. Could she have taken it?

No way!



<o.6% chance

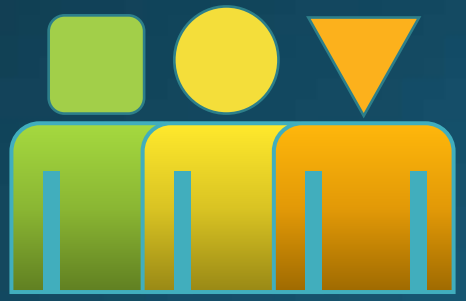
Overcoming

Challenges to Precision Dosing

Patient-Level Challenges

30% vancomycin troughs are appropriately timed

All undetectable voriconazole was after outpatient dosing



98% inter- and 66% intra-individual variability in voriconazole AUC among children <2 years of age

Patient-Level Solutions

"Clinical Pharmacometrics" is the application of quantitative modeling and simulation tools for the purpose of optimizing therapy in an individual patient.

Patient-Level Solutions – Clinical PMx

Robust to timing of samples

Model probability of adherence

Control inter- and compensate for intra-individual variability

Process challenges

Formulation restrictions

Rapidly available drug concentrations

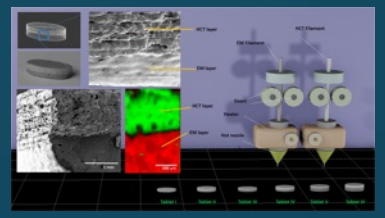
Software tools

Poorly defined concentration targets

Reimbursement

Lack of expertise

Process solutions



Novel formulations

HPLC, immuno, LC-MS, field sampling, wearables

More on this…

Studies, package insert

More on this…

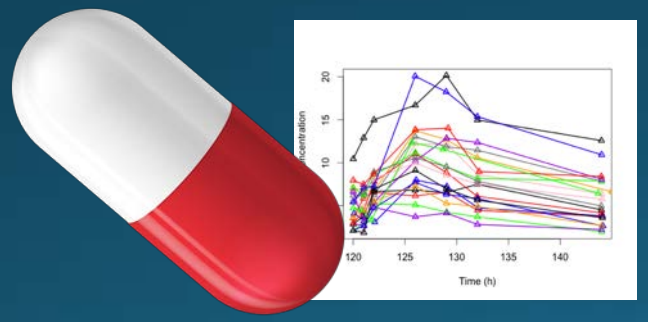
Training

Payment (USA)

- Z51.81 – Any therapeutic drug monitoring
- Z79.xxx – Specific long term therapy
  - E.g. *Z79.2* long term (current) use of antibiotics
- Code for underlying diagnosis
- Must be in the context of a face-to-face encounter with the patient
  - Physicians use Evaluation/Management (E/M) codes
  - Pharmacists use Medication Therapy Management (MTM) codes

Regulation

Path for software marketing approval

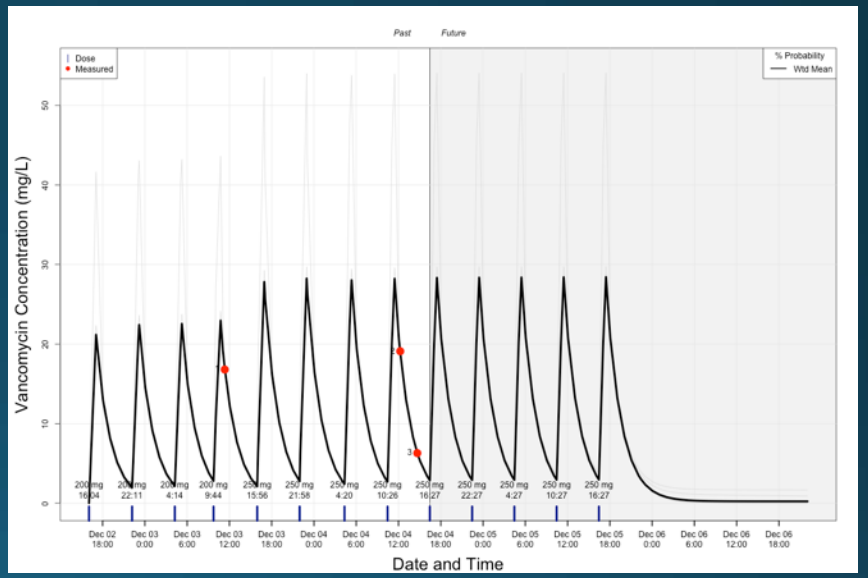


Approved doses or exposures?

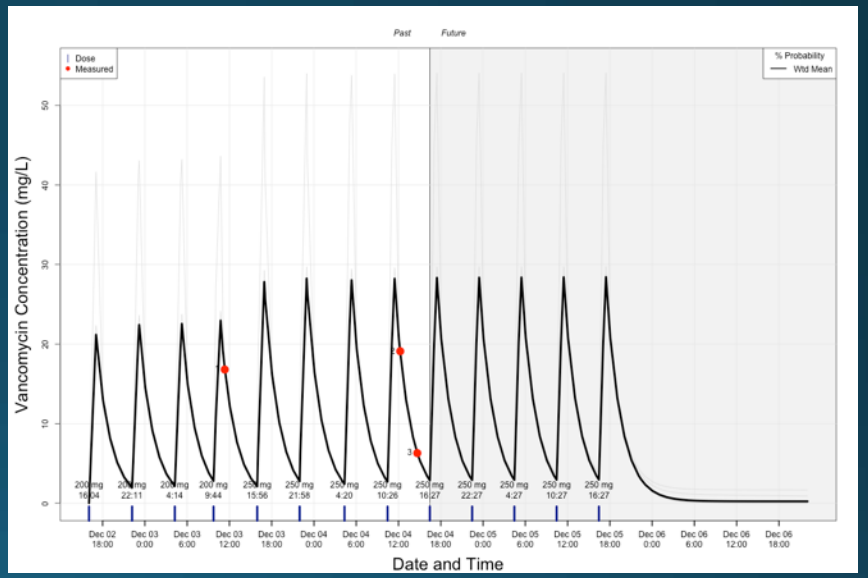
Current thinking

- "Clinical and Patient Decision Support Software, Draft Guidance for Industry and Food and Drug Administration Staff ", Dec 8, 2017
  - Section IV, A: Examples of CDS Functions that are not Devices
    - Line 290: Software that provides health care professionals with recommendations on the use of a prescription drug that are consistent with the FDA-required labeling.

Predicting/forecasting

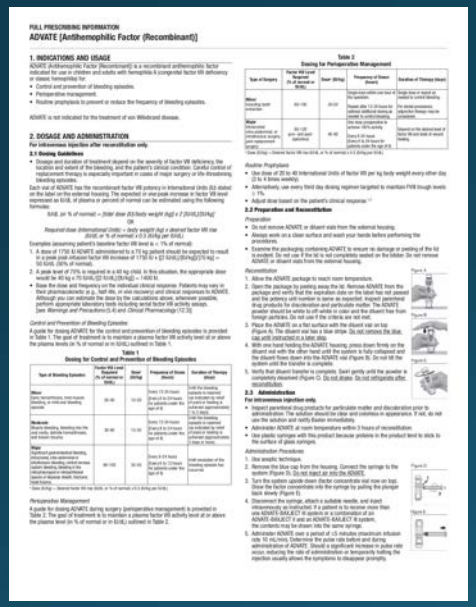


Optimizing/recommending



Rx

X



FULL PRESCRIBING INFORMATION

ADVATE [Antihemophilic Factor (Recombinant)]

1. INDICATIONS AND USAGE

ADVATE (Antihemophilic Factor [Recombinant]) is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for:

- Control and prevention of bleeding episodes.
- Perioperative management.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ADVATE is not indicated for the treatment of von Willebrand disease.

2. DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.

2.1 Dosing Guidelines

- Dosage and duration of treatment depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.

Each vial of ADVATE has the recombinant factor VIII potency in International Units (IU) stated on the label on the external housing. The expected in vivo peak increase in factor VIII level expressed as IU/dL of plasma or percent of normal can be estimated using the following formulas:

IU/dL (or % of normal) = [total dose (IU) body weight (kg)] x 2 (IU/dL)/(IU/kg)

OR

Required dose (international Units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Examples (assuming patient's baseline factor VIII level is < 1% of normal):

1. A dose of 1750 IU ADVATE administered to a 70 kg patient should be expected to result in a peak post-infusion factor VIII increase of 1750 IU ÷ [(2 IU/dL)/(IU/kg)] x 70 kg] = 50 IU/dL (50% of normal).
2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 40 kg x 70 IU/dL ÷ [2 IU/dL/(IU/kg)] = 1400 IU.
- Base the dose and frequency on the individual clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to ADVATE. Although you can estimate the dose by the calculations above, whenever possible, perform appropriate laboratory tests including aerial factor VIII activity assays. (see *Warnings and Precautions* (5.4) and *Clinical Pharmacology* (12.3))

Control and Prevention of Bleeding Episodes:

A guide for dosing ADVATE for the control and prevention of bleeding episodes is provided in Table 1. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1.

Table 1

Dosing for Control and Prevention of Bleeding Episodes

Type of Bleeding Episodes	Factor VIII Level Required (% of normal or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding	30-60	10-20	Every 12-24 hours. Every 6 to 10 hours for patients under the age of 6.	Until the bleeding episode is resolved, as indicated by relief of pain or healing or (where appropriate) radiographic improvement.
Moderate Muscle bleeding, bleeding into the joints, oral cavity, definite hemorrhage, and wound trauma	30-60	15-30	Every 12-24 hours. Every 6 to 10 hours for patients under the age of 6.	
Major Significant gastrointestinal bleeding, intracranial hemorrhage, intracranial bleeding, central nervous system bleeding, bleeding in the throat with potential airway compromise, trauma or fracture, shock, fulminant bleeding	60-100	30-40	Every 6-24 hours. Every 6 to 10 hours for patients under the age of 6.	Until resolution of the bleeding episode has occurred.

Perioperative Management

A guide for dosing ADVATE during surgery (perioperative management) is provided in Table 2. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma level (in % of normal or in IU/dL) outlined in Table 2.

Table 2

Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor including tooth extraction	30-60	20-50	Single dose within one hour of the operation. Repeat after 12-24 hours for optimal wound healing as needed to control bleeding.	Single dose or repeat as needed to control bleeding.
Major (Minor/other intra-abdominal, or intracranial procedure; joint replacement surgery)	80-100 (pre- and post-operatively)	40-60	Every 8-24 hours (Every 6 to 10 hours for patients under the age of 6).	For dental procedures, adjunctive therapy may be necessary. Repeat on the desired level of factor VIII until total dose of wound healing.

Routine Prophylaxis

- Use dose of 20 to 40 International Units of factor VIII per kg body weight every other day (3 to 4 times weekly).
- Alternatively, use every third day dosing regimen targeted to maintain FVIII trough levels ≥ 1%.
- Adjust dose based on the patient's clinical response.[1,2]

2.2 Preparation and Reconstitution

Preparation

- Do not remove ADVATE or diluent vials from the external housing.
- Always work on a clean surface and wash your hands before performing the procedures.
- Examine the packaging containing ADVATE to ensure no damage or peeling of the lid is evident. Do not use if the lid is not completely seated on the blister. Do not remove ADVATE or diluent vials from the external housing.

Reconstitution

1. Allow the ADVATE package to reach room temperature.
2. Open the package by peeling away the lid. Remove ADVATE from the package and verify that the expiration date on the label has not passed and the potency unit number is same as expected. Inspect parenteral drug products for discoloration and particulate matter. The ADVATE powder should be white to off-white in color and the diluent free from visible particulates. Do not use if the criteria are not met.
3. Place the ADVATE on a flat surface with the diluent vial on top (Figure A). The diluent vial has a blue shrink. Do not remove the blue cap until instructed in a later step.
4. With one hand holding the ADVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADVATE vial (Figure B). Do not lift the system until the transfer is complete.
5. Verify that diluent transfer is complete. Swirl gently until the powder is completely dissolved (Figure C). Do not shake. Do not refrigerate after reconstitution.

2.3 Administration

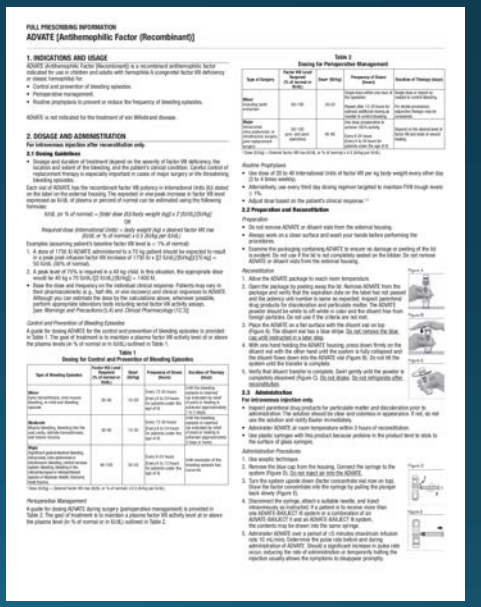
For intravenous injection only.

- Inspect parenteral drug products for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Baxter immediately.
- Administer ADVATE at room temperature within 3 hours of reconstitution.
- Use plastic syringes with this product because proteins in the product tend to stick to the surface of glass syringes.

Administration Procedures

1. Use aseptic technique.
2. Remove the blue cap from the housing. Connect the syringe to the system (Figure D). Do not inject air into the ADVATE.
3. Turn the system upside down (factor concentrate vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure E).
4. Disconnect the syringe, attach a suitable needle, and inject intravenously as indicated. If a patient is to receive more than one ADVATE dose, ADVATE in syringes or a combination of an ADVATE 40IU/LET II and an ADVATE 4IU/LET III system, the contents may be drawn into the same syringe.
5. Administer ADVATE over a period of ≤ 5 minutes (maximum infusion rate 10 mL/min). Determine the pulse rate before and during administration of ADVATE. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

Device



FULL PRESCRIBING INFORMATION

ADVATE [Antihemophilic Factor (Recombinant)]

Not Device

How do we change the label?

"Patients may require dosages other than those listed in Sections 2 (Dosage and Administration) and 8 (Use in Specific Populations) to achieve acceptably safe and effective concentrations within the range of those studied and reported in Section 12 (Clinical Pharmacology). Dosage adjustments should be based upon measured drug concentrations and/or relevant patient characteristics."

What PK data should be in PI?

- CFR § 201.57(c)(13)(i)(C) governing content of PK section for package inserts:
  - *12.3 Pharmacokinetics.* This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), pertinent half-lives (t1/2), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant.

What PK data ARE there?

	Adult n=50	Peds n=50
Tmax*	40	7
Cmax*	23	12
AUC*	10	8
Vd*	22	8
Time-con curve	6	0
Cmin*	6	3
CL*	26	18
Thalf*	44	23

*Named in CFR

- Reviewed package inserts of 50 drugs for which FDA granted pediatric exclusivity under BPCA and relabeled
- Excluded topical agents and those with no discussion of pediatric dosing
- Abstracted from the pharmacokinetics sub-section in the clinical pharmacology section

What guidance is there?

- FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, December 2016
  - Descriptive and generally without specific data items, e.g. guidance on Absorption section does not mention either Tmax or Cmax

Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C_{max} µg/mL	C_{min} µg/mL	T_{max} hrs	AUC * µg • h/mL	$t_{1/2}$ hrs	CL mL/min
400 mg tablet						
single dose †	8.10 (1.83)	---	1.52 (1.01)	55.10 (25.00)	5.20 (1.50)	146 (67)
every 12 hours	11.00 (4.37)	3.08 (2.25)	1.12 (0.47)	73.40 (33.50)	4.69 (1.70)	110 (49)
600 mg tablet						
single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV injection ‡						
single dose	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600 mg oral suspension						
single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

* AUC for single dose = $AUC_{0-\infty}$; for multiple-dose = $AUC_{0-\tau}$

† Data dose-normalized from 375 mg

‡ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life; CL = Systemic clearance

Zyvox® (linezolid) package insert

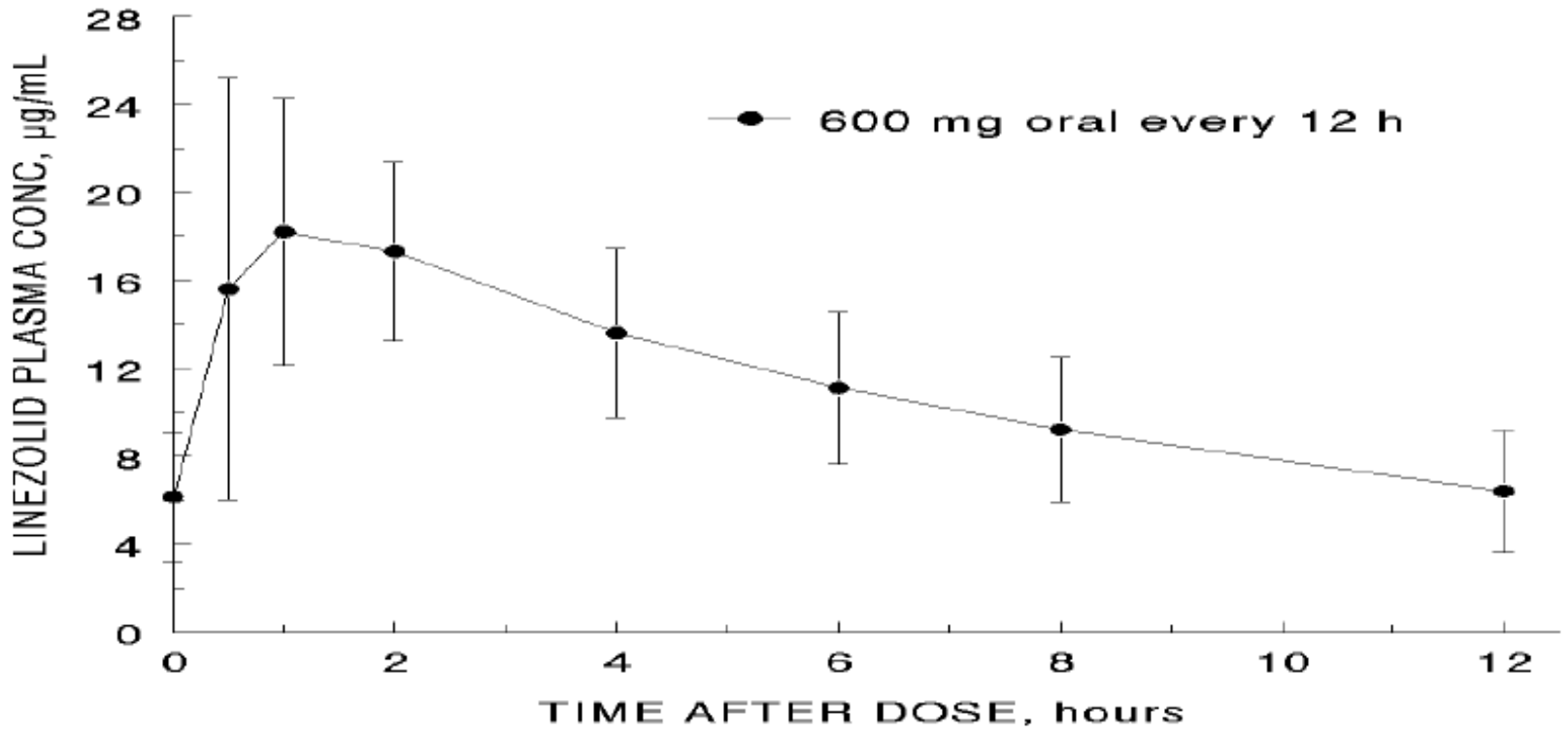


Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Table 2. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg•h/mL	$t_{1/2}$ hrs	CL mL/min/kg
Neonatal Patients					
Pre-term** < 1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term*** < 1 week (N=10)†	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term*** ≥ 1 week to ≤ 28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients > 28 days to < 3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years‡ (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects§ (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

* AUC = Single dose $AUC_{0-\infty}$

** In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

*** In this data set, "full-term" is defined as ≥34 weeks gestational age

† Dose of 10 mg/kg

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

C_{max} = Maximum plasma concentration; V_{ss}= Volume of distribution, AUC = Area under concentration-time curve; $t_{1/2}$ = Apparent elimination half-life; CL = Systemic clearance normalized for body weight

The Future: Emphasize exposure

- Doses in PI sections 2 and 8 become starting doses
- Standardize reported PK characteristics
- Mandate exposure-response section
- Link to de-identified subject-level data in FDA repository
  - Sponsor companies must share after approval
  - Reasons to withhold are reduced
- Flexible dosing is permissible

Call for a Precision Dosing Advisory group

- Mission: To provide regulatory support for precision dosing
- Method: Revise/create relevant FDA guidance documents and package insert content
- Composition/representation
  - Physician/Pharmacist organizations
  - Academia
  - Medical Software industry
  - Pharmaceutical industry
  - Electronic medical record vendors
  - Insurers
  - Government (regulatory, quality, medical, scientific)

Citations

1. Neely M. Scalpels not hammers: The way forward for precision drug prescription. Clin Pharmacol Ther. 2017 Mar 1;101(3):368–72.

2. Neely M, Jelliffe R. Practical, individualized dosing: 21st century therapeutics and the clinical pharmacometrician. J Clin Pharmacol. 2010 Jul;50(7):842–7.

3. Neely M, Jelliffe R. Practical therapeutic drug management in HIV-infected patients: use of population pharmacokinetic models supplemented by individualized Bayesian dose optimization. J Clin Pharmacol. 2008 Sep;48(9):1081–91.