U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Modeling and Simulation to Support Appropriate Use of Long-Acting Antipsychotics

Hao Zhu, Ph.D.,
Division of Pharmacometrics,
OCP/OTS/CDER/FDA
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Disclaimer:
1. I have no conflict of interest to report.
2. The views expressed are my personal views and may not represent the position of the US FDA.

Outline

- **Background & Introduction**
  - Long acting injectables (LAIs) for patients with psychiatric diseases
  - Examples of LAIs
- **Modeling and Simulation for LAIs**
  - Role of M&S for LAIs with Examples from Invega Sustenna ®
    - To support new dosing regimens
    - To define dosing windows
    - To select reinitation plans
    - To adjust dosing regimes in subgroups
- **Take Home Messages**

Background

- Psychiatric diseases, such as schizophrenia and bipolar disorder, are severe debilitating mental disorders affecting patients' daily function and social interaction.
- Long-acting injectable (LAI) anti-psychiatric products have been developed & marketed in recent years.
  - Chronic treatment is essential to prevent relapse and to control symptoms.
  - Compliance is a common problem in patients with schizophrenia or bipolar disorder.

Introduction

Examples of Marketed Long-Acting Injectable Anti-psychotics

Compound	Product	Dosing Regimen
Aripiprazole	Abilify Maintena ®	400 mg + 10/20 mg oral daily × 14 days & 400 /300 mg Q monthly
Aripiprazole Lauroxil	Aristada ® Aristada Initio ®	(1) Aristada Initio® 675 mg + 30 mg oral + Aristada® × 1 (2) Aristada ® + oral × 21 days & 441, 662, 882 mg Q monthly, or 882 mg Q 6 Wk, or 1064 mg Q 2 months.
Olanzapine	Zyprexa Relprevv ®	150, 210, 300 mg Q 2Wk, or 300, 405 mg Q 4Wk
Paliperidone	Invega Sustenna ®	234 mg day 1 + 156 mg day 8 & 39 – 234 mg Q monthly
Paliperidone	Invega Trinza ®	273 – 819 mg Q 3 months (Following Invega Sustenna ® for at least
Risperidone	Risperdal Consta ®	25 mg Q 2 Wk

Modeling and Simulation for LAIs

- To optimize dosing regimens.
- To define dosing windows.
- To select reinitiation plans.
- To adjust dosing regimens in patient subgroups.

Invega Sustenna ®

Slow dissolution consistent with the ***particle size*** and ***low solubility***.

Paliperidone palmitate is an LAI:

- Indicated for the treatment of schizophrenia and schizoaffective disorder in adults

ADME Features

Process	Key Features
Absorption	T max = 13 days, A single dose releases the drug from Day 1 to Day 126.
Distribution	Vd= 391 L, protein binding = 74%
Metabolism	Paliperidone palmitate hydrolyzed into paliperidone.
Excretion	59% of the dose excreted into urine as unchanged drug. T ½ = 25-49 days

*: Invega Sustenne ® U.S. Package Insert

Dosing Regimen (1)

- Short-term schizophrenia trials (Section 14 of the U.S. package insert)

Clinical Trial	Dosing
Study 1	3 dose groups: (234 mg + 39 mg Q 4 Wk, 156 mg Q 4 Wk, or 234 mg Q 4 Wk) vs. Placebo
Study 2	3 dose groups: (78 mg Q 4 Wk, 156 mg Q 4 Wk, 234 mg Q 4Wk) vs. Placebo
Study 3	3 dose groups: (39 mg Q 4 Wk, 78 mg Q 4 Wk, 156 mg Q 4 Wk) vs. Placebo
Study 4	2 dose groups: (78 mg Q 4 Wk, 156 mg Q 4 Wk) vs. Placebo

Note: Study 2-3 included only **maintenance doses**. Study 1 included ***1*** loading dose + **maintenance doses**.

Dosing Regimen (2)

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	INVEGA SUSTENNA® (39 mg/4 weeks)*	86.9 (11.99)	-11.2 (1.69)	-5.1 (-9.01, -1.10)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	86.2 (10.77)	-14.8 (1.68)	-8.7 (-12.62, -4.78)
	INVEGA SUSTENNA® (234 mg/4 weeks)*	88.4 (11.70)	-15.9 (1.70)	-9.8 (-13.71, -5.85)
	Placebo	86.8 (10.31)	-6.1 (1.69)	--
Study 2[b]	INVEGA SUSTENNA® (78 mg/4 weeks)	89.9 (10.78)	-6.9 (2.50)	-3.5 (-8.73, 1.77)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.1 (11.66)	-10.4 (2.47)	-6.9 (-12.12, -1.68)
	Placebo	92.4 (12.55)	-3.5 (2.15)	--
Study 3	INVEGA SUSTENNA® (39 mg/4 weeks)*	90.7 (12.25)	-19.8 (2.19)	-6.6 (-11.40, -1.73)
	INVEGA SUSTENNA® (78 mg/4 weeks)*	91.2 (12.02)	-19.2 (2.19)	-5.9 (-10.76, -1.07)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	90.8 (11.70)	-22.5 (2.18)	-9.2 (-14.07, -4.43)
	Placebo	90.7 (12.22)	-13.3 (2.21)	--
Study 4	INVEGA SUSTENNA® (78 mg/4 weeks)*	88.0 (12.39)	-4.6 (2.43)	-11.2 (-16.85, -5.57)
	INVEGA SUSTENNA® (156 mg/4 weeks)*	85.2 (11.09)	-7.4 (2.45)	-14.0 (-19.51, -8.58)
	Placebo	87.8 (13.90)	6.6 (2.45)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Because an insufficient number of subjects received the 234 mg/4 weeks dose, results from this group are not included.

* $p<0.05$ (Doses statistically significantly superior to placebo).

3 doses were superior to placebo

156 mg Q 4 Wk was superior to placebo

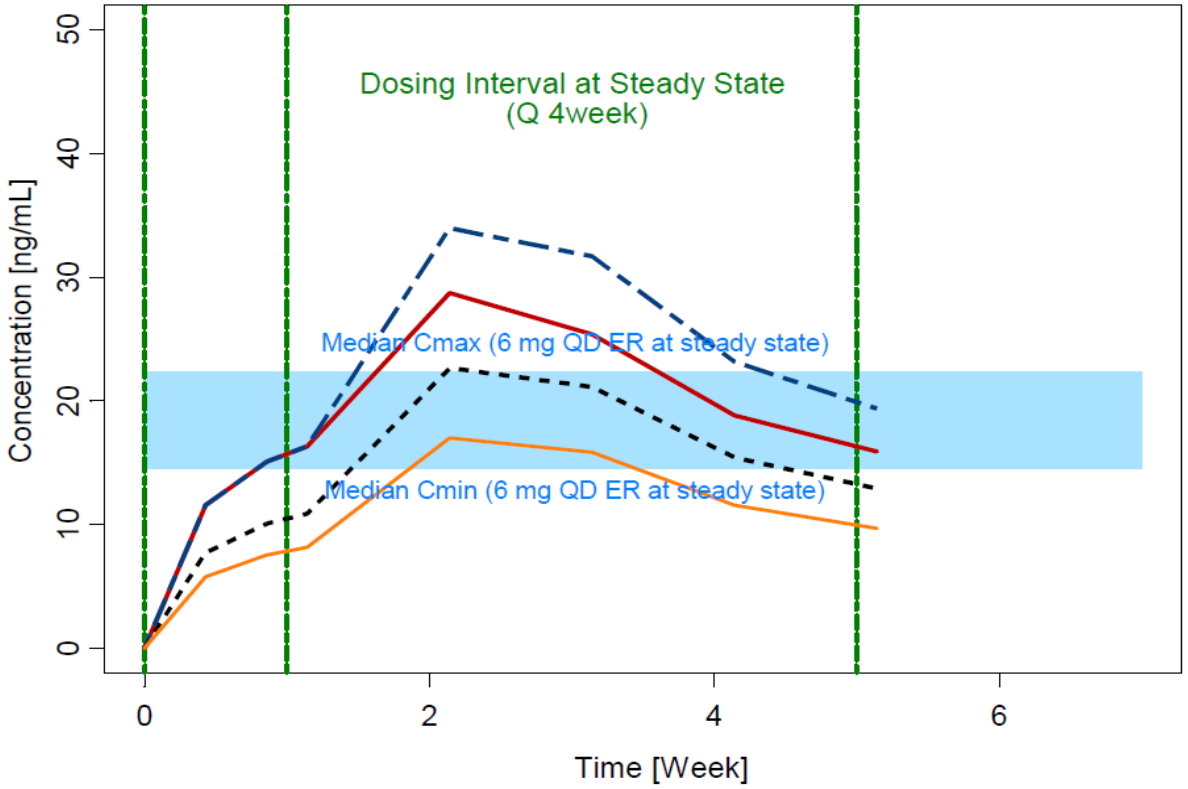
3 doses were superior to placebo

2 doses were superior to placebo

Dosing Regimen (3)

- Approved Dosing Regimen: **234 mg Day 1 + 156 mg Day 8 + 39 – 234 mg Monthly**

PK Simulation to assess the initial dosing regimens



Approved Dosing Regimen

Target Exposure Range

Safety margin (Study 3007):
150 mg (Day 1) + 150 mg (Day 8)

Alternative initial dosing regimens

75 mg (Day1) + 75 mg (Day8)

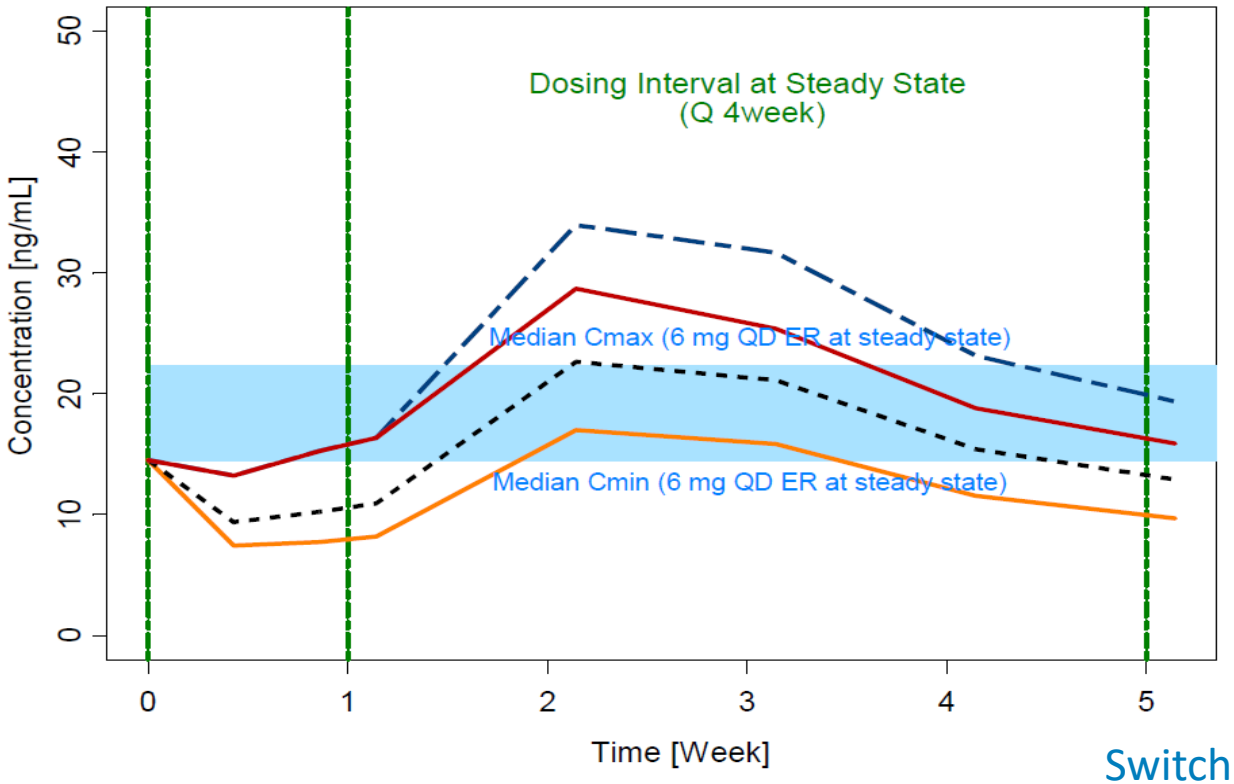
100 mg (Day 1) + 100 mg (Day 8)

No initial treatment (i.e., $C_0 = 0$), desirable exposure can be achieved by the end of the first week.

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Dosing Regimen (4)

PK Simulation to assess the initial dosing regimens



Approved Dosing Regimen

Target Exposure Range

Safety margin (Study 3007):
150 mg (Day 1) + 150 mg (Day 8)

Alternative initial dosing regimens

75 mg (Day1) + 75 mg (Day8)

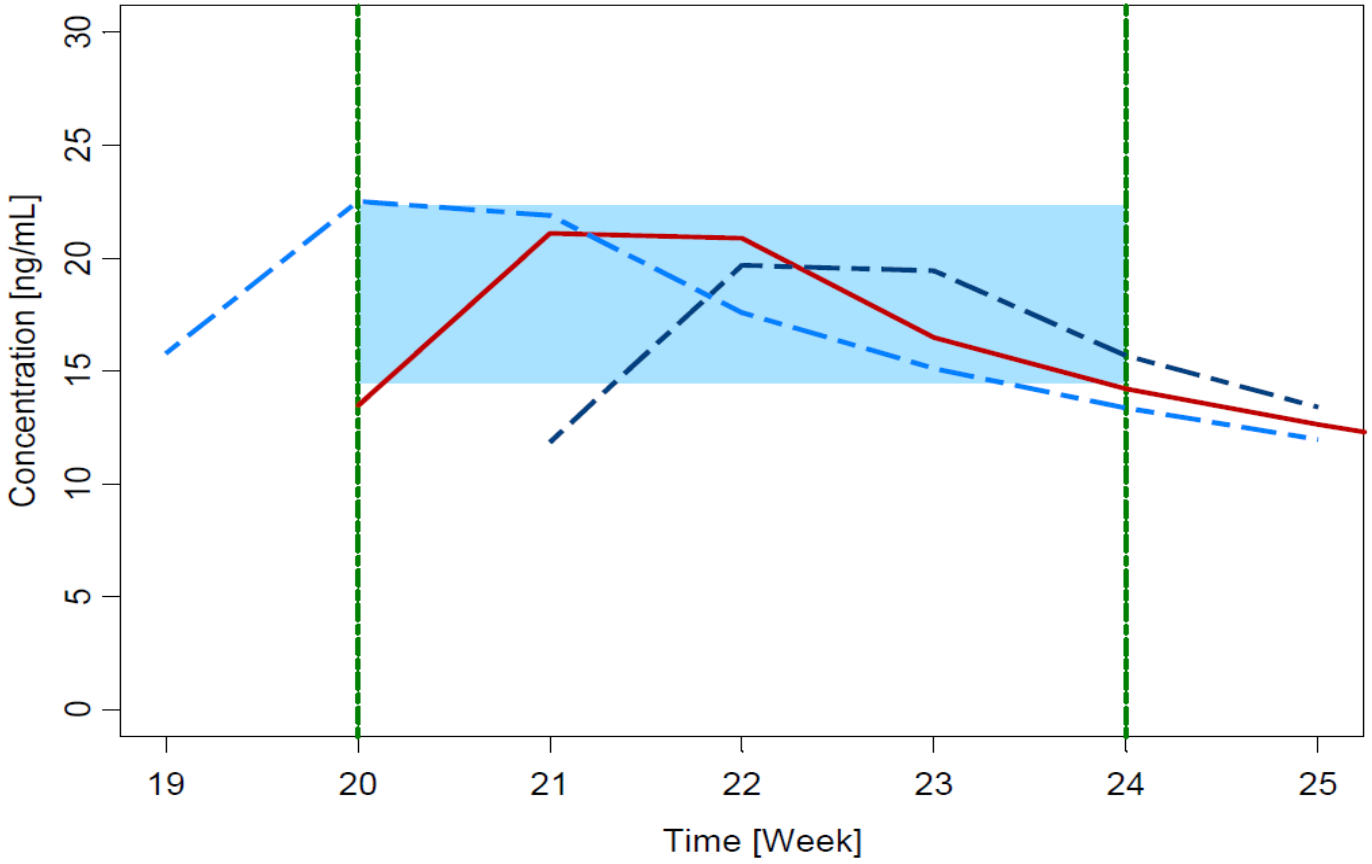
100 mg (Day 1) + 100 mg (Day 8)

Switching from a stable treatment (i.e., C_0 = C trough), desirable exposure can be achieved within the first week.

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Dosing Window

Dosing	Scheduled Dosing Time	Dosing Window
Second Initial Dosing	Day 8	± 4 Days (Initial Approval was ± 2 days)
Maintenance Dosing	Monthly	± 7 Days



Target Exposure Range

Scheduled Dosing (Monthly)

Delayed Dosing (Monthly + 7 Days)

Early Dosing (monthly – 7 Days)

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Reinitiation Plan for Patients with Missing Doses

TIMING OF MISSED SECOND INITIATION DOSE	DOSING
Less than 4 weeks since first injection	**Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.** 1. It is recommended to administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of the timing of the second injection). 2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since first injection	**Resume dosing with two injections of 156 mg in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since first injection	**Restart dosing with recommended initiation** *(see Section 2.2, Table 1)*: 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.

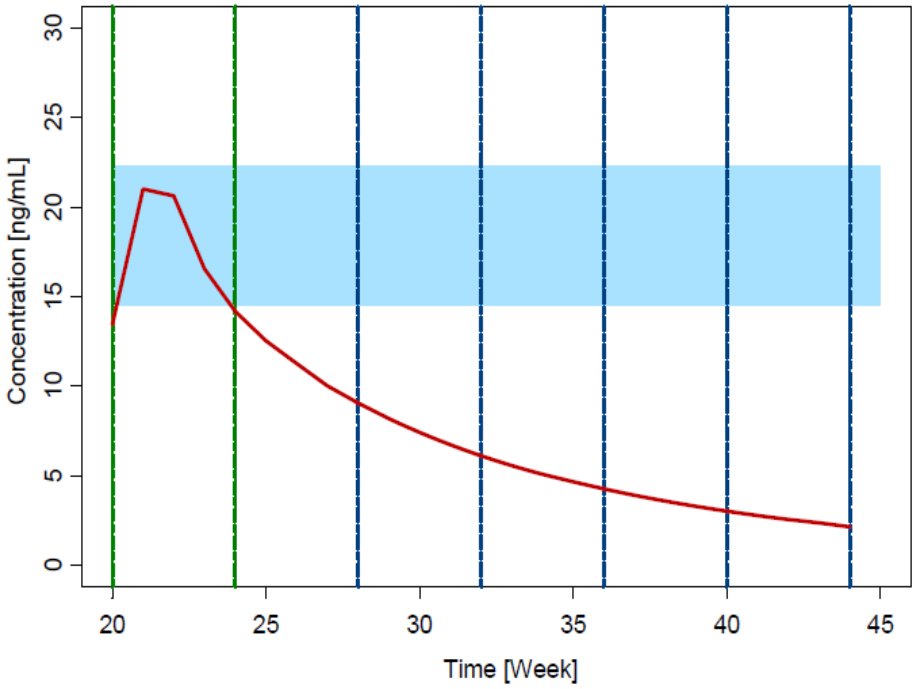
Missing Loading Dose

TIMING OF MISSED MAINTENANCE DOSE	DOSING
4 to 6 weeks since last injection	**Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals.**
More than 6 weeks to 6 months since last injection	**Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later at the same dose. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	**Restart dosing with recommended initiation** *(see Section 2.2, Table 1)*: 1. Administer a 234 mg deltoid injection on Day 1. 2. Administer a 156 mg deltoid injection 1 week later. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

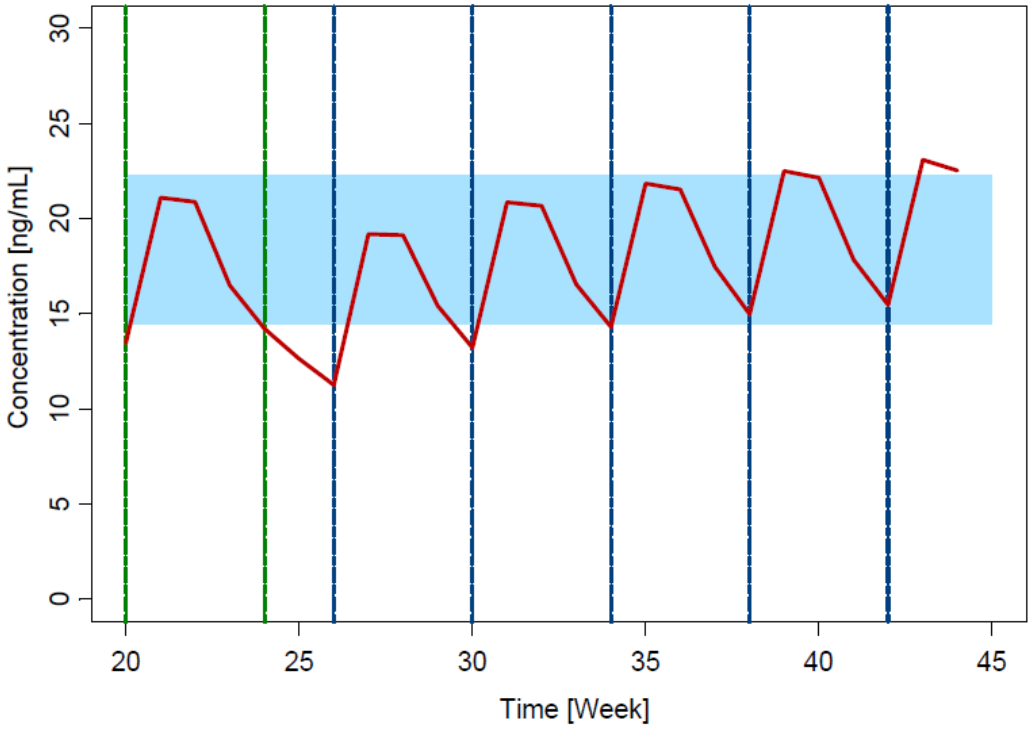
Missing Maintenance Dose

Invega Sustenna ® U.S. Package Insert
<https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022264Orig1s033lbl.pdf>

Reinitiation of Treatment for Patients with Missing Doses



With no reinitation



With proposed reinitiation

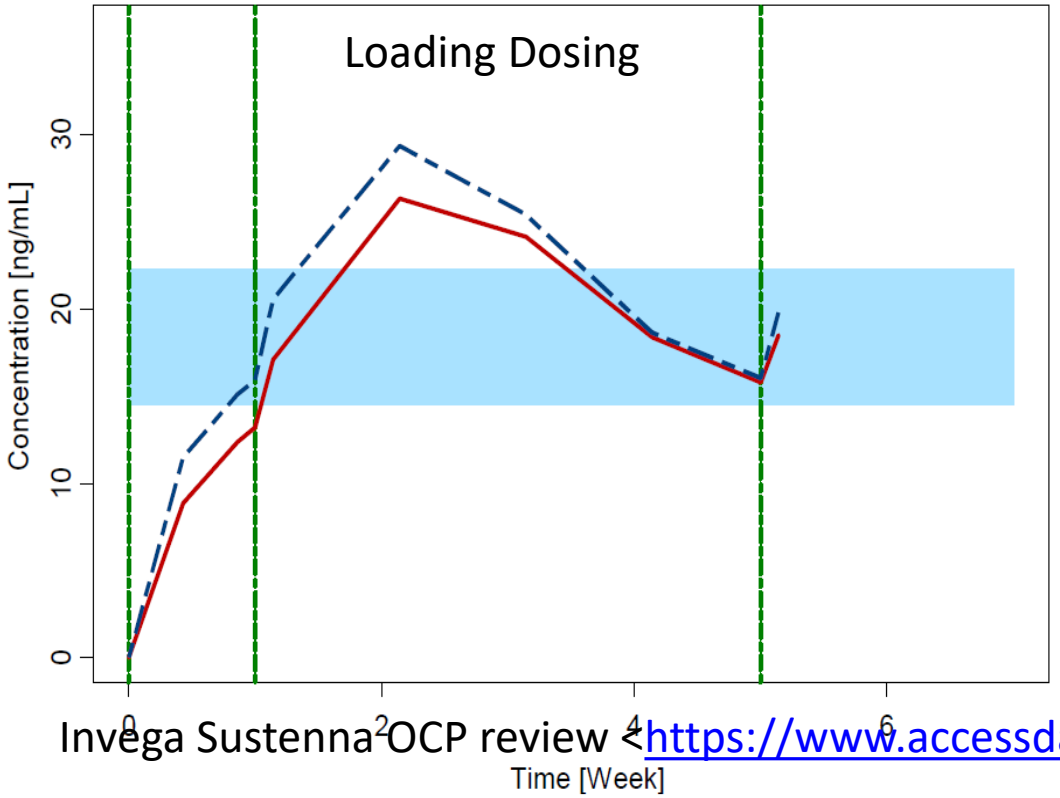
To assess reinitation of treatment for patients with missing dose between 6 weeks to 6 months

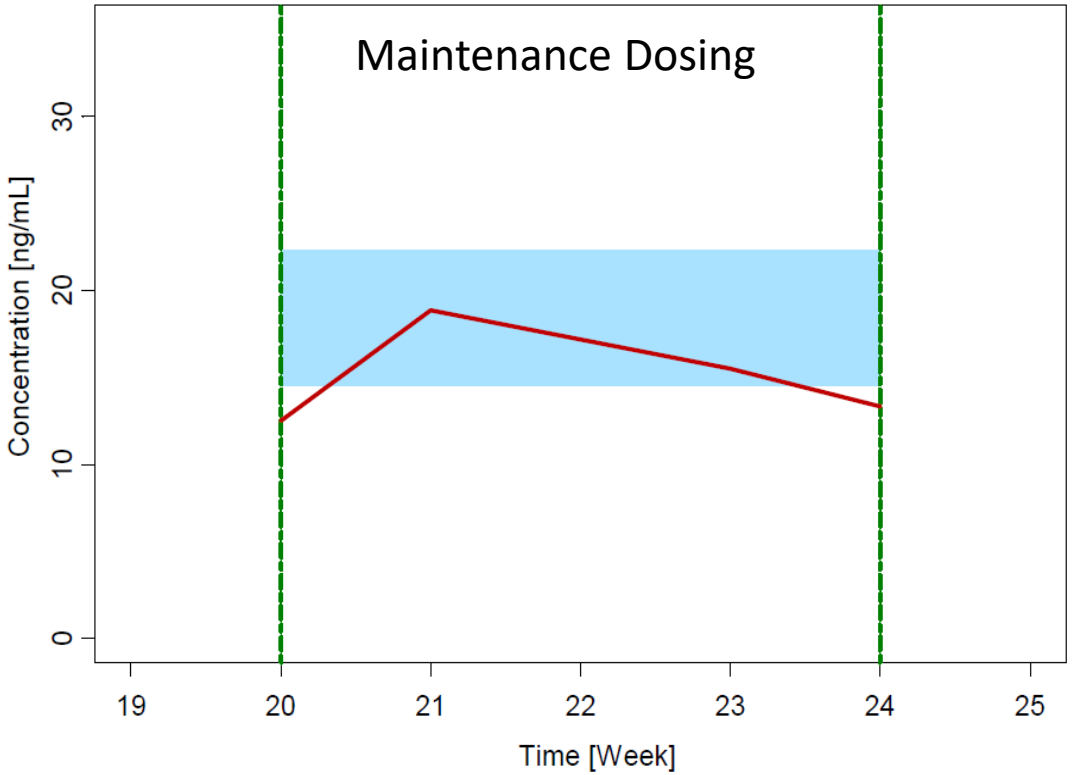
Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Dosage in Mild Renal Impairment Patients

Renal Impairment

INVEGA SUSTENNA® has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), initiate INVEGA SUSTENNA® with a dose of 156 mg on treatment day 1 and 117 mg one week later. Administer both doses in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.





Target Exposure Range

Labeled Dosing

Safety Margin

Invega Sustenna OCP review <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022264s000clinpharmr.pdf>

Take Home Message

- Modeling and simulation are essential tools to facilitate the development of long-acting injectable products.
  - To support new dosing regimens
  - To define dosing windows
  - To select reinitation plans
  - To adjust dosing regimes in subgroups

Acknowledgement

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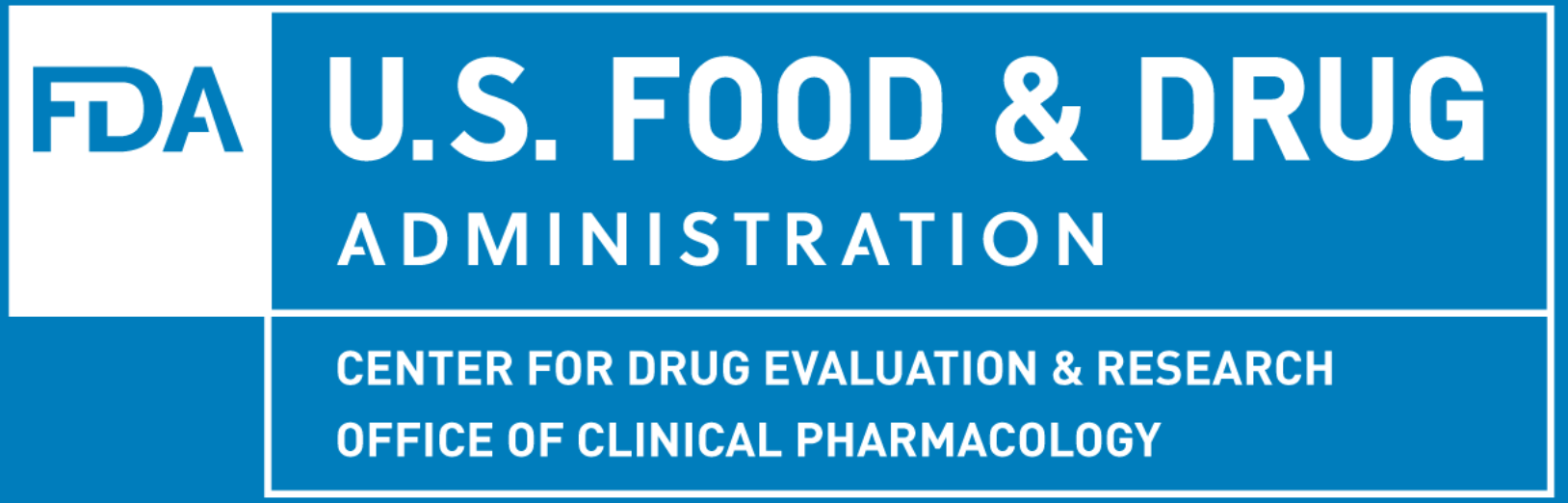
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