

<b>NDA Number:</b>	22047
<b>Submission Type</b>	Efficacy Supplement/S029
<b>Applicant Name</b>	AstraZeneca Pharmaceuticals LP
<b>Submission Dates</b>	10/29/2012
<b>Brand Name</b>	Quetiapine
<b>Generic Name</b>	Seroquel XR
<b>Dosage Form</b>	Extended Release Tablets
<b>Dosage Strength</b>	50 mg, 150 mg, 200 mg, 300 mg, 400 mg
<b>Proposed Indication</b>	Schizophrenia and Bipolar Mania
<b>OCP Review Team</b>	Islam R. Younis, Ph.D., Hao Zhu, Ph.D., Yaning Wang, Ph.D.

## 1. Executive Summary

Quetiapine (QTP) is an atypical antipsychotic with an immediate release (IR) and extended release (XR) formulations. Both formulations are approved in adults for the treatment of schizophrenia and bipolar mania in addition to other indications. The IR formulation is also approved in pediatrics for the treatment of schizophrenia in adolescents 13 – 17 years of age and the treatment of bipolar mania in children and adolescents 10 – 17 years of age. The XR formulation was developed to improve the convenience of QTP treatment for patients by introducing once-daily administration. The XR formulation was not evaluated in pediatrics patients with schizophrenia or bipolar mania (Table 1)

**Table 1.** Quetiapine NDAs approval history by population and formulation.

Formulation (NDA)	IR (NDA 020639)		XR (NDA 022047)	
Dosage Strength	25, 50, 100, 200, 300, 400 mg		200, 300, 400 mg	
Population	Adult	Pediatrics	Adult	Pediatrics
Schizophrenia	S-000 (09/26/1997)	S-046 (12/02/2009)	S-000 (05/17/2007)	Not Approved
Bipolar Mania	S-016 (01/12/2004)	S-045 (12/02/2009)	S-007 (10/08/2008)	Not Approved

The purpose of this review is to provide recommendation on approving QTP XR formulation for the treatment of schizophrenia and bipolar mania in pediatrics 10 to 17 years of age without the need for pharmacokinetics or efficacy trials. To provide recommendations, the clinical pharmacology review team used a totality of evidences approach through leveraging prior QTP exposure, efficacy, and safety information following the administration of both formulations in pediatrics and adults patients.

QTP approved doses are similar across formulations and patient populations. QTP is titrated to effect and the approved dose range is 400 to 800 mg/day except for IR in adult schizophrenia where the approved dose range is 150 to 750 mg/day.

In adult patients, treatment effect and safety profile is similar across the two formulations for both schizophrenia and bipolar mania. Also, QTP AUC is similar following the

administration of the IR and XR formulations with a geometric mean ratio (GMR (XR/IR)) of 1.04 and corresponding 90%CI of (0.92,1.19). QTP  $C_{max}$  is slightly lower following the administration of the XR formulation with GMR (XR/IR) of 0.87 and 90%CI of (0.77, 0.99). QTP plasma profile is not similar following the administration of XR QD (one peak) and IR BID (two peaks) formulations in adult patients. Based on the above, it is apparent that the IR and XR formulation produces similar exposure and effects in adults and AUC is the major exposure parameter that appears to affect QTP efficacy and safety.

In pediatric patients following the administration of the IR formulation, QTP efficacy is similar to that obtained in adults for both schizophrenia and bipolar mania. On the other hand, QTP exposure is lower in pediatric patients compared to adult patients. Dose and weight normalized exposure parameters are approximately 40% lower in pediatrics relative to adults. Geometric mean ratio (pediatrics/adults) of AUC is 0.59 [90% CI (0.5, 0.7)] and of  $C_{max}$  is 0.6 [90%CI (0.53, 0.72)]. Therefore, reduction in exposure in pediatrics due to higher clearance does not translate into significant changes in efficacy. The safety profile of QTP following eight weeks exposure to the XR formulation (150 to 300 mg/ day) in 92 pediatric, 10 to 17 years of age, patients with bipolar depression was similar to safety profile observed in pediatrics following the IR formulation administration.

The absorption of drugs following the administration of XR formulation is expected to be similar in pediatrics 10 to 17 years of age and adults. (b) (4)

Similarity in pharmacokinetic behavior for XR formulations between adults and pediatrics 10 – 17 years of age was observed for other drugs such as paliperidone, divalproex sodium, and lamotrigine.

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## 1.1 Recommendations

The Office of Clinical Pharmacology recommends approving QTP XR formulation for the treatment of schizophrenia and bipolar mania in pediatric formulation without the need for a dedicated clinical pharmacokinetic or efficacy trial based on the following reasons:

1. Similarity of the approved dose of QTP IR formulation in adults and pediatrics.
2. Similarity in treatment effect of QTP in adults (IR and XR) and pediatrics (IR).

3. Similarity of QTP AUC the QTP IR and XR formulations.
4. Similarity in pharmacokinetic behavior for XR formulations for other compounds between adults and pediatrics 10 – 17 years of age.
5. Similarity of safety profile following the administration of QTP XR and IR formulations to pediatrics 10 to 17 years of age.

The above mentioned evidences provide sufficient foundation to believe that QTP XR formulation will deliver similar exposure and efficacy/safety as QTP IR formulation in pediatrics 10 to 17 years of age. Moreover, it will be unethical to request a clinical pharmacokinetic or efficacy trial in pediatrics without any perceived benefits. This conclusion is supported by the guiding principles for the conduct of in vivo bioavailability study outlined in CFR 320.25 “the basic principle in an in vivo bioavailability study is that no unnecessary human research should be done”.

### **1.2 Labeling Recommendations**

Quetiapine XR label should include similar pediatric indications as quetiapine IR formulation label.

## 2. Question Based Review

### 2.1 Specific Questions

#### 2.1.1 Is there sufficient evidences to support approving QTP XR formulation for the treatment of schizophrenia and bipolar mania in pediatrics 10 to 17 years of age?

Yes. The evidences listed below provide sufficient foundation to predict similar exposure and efficacy of QTP XR and QTP IR in pediatrics 10 to 17 years of age:

#### I. Similarity of approved doses:

QTP IR is approved for schizophrenia and bipolar mania in adults and pediatrics in the same dose range (Table 2). More over, QTP XR formulation is approved in the same dose range as the IR formulation.

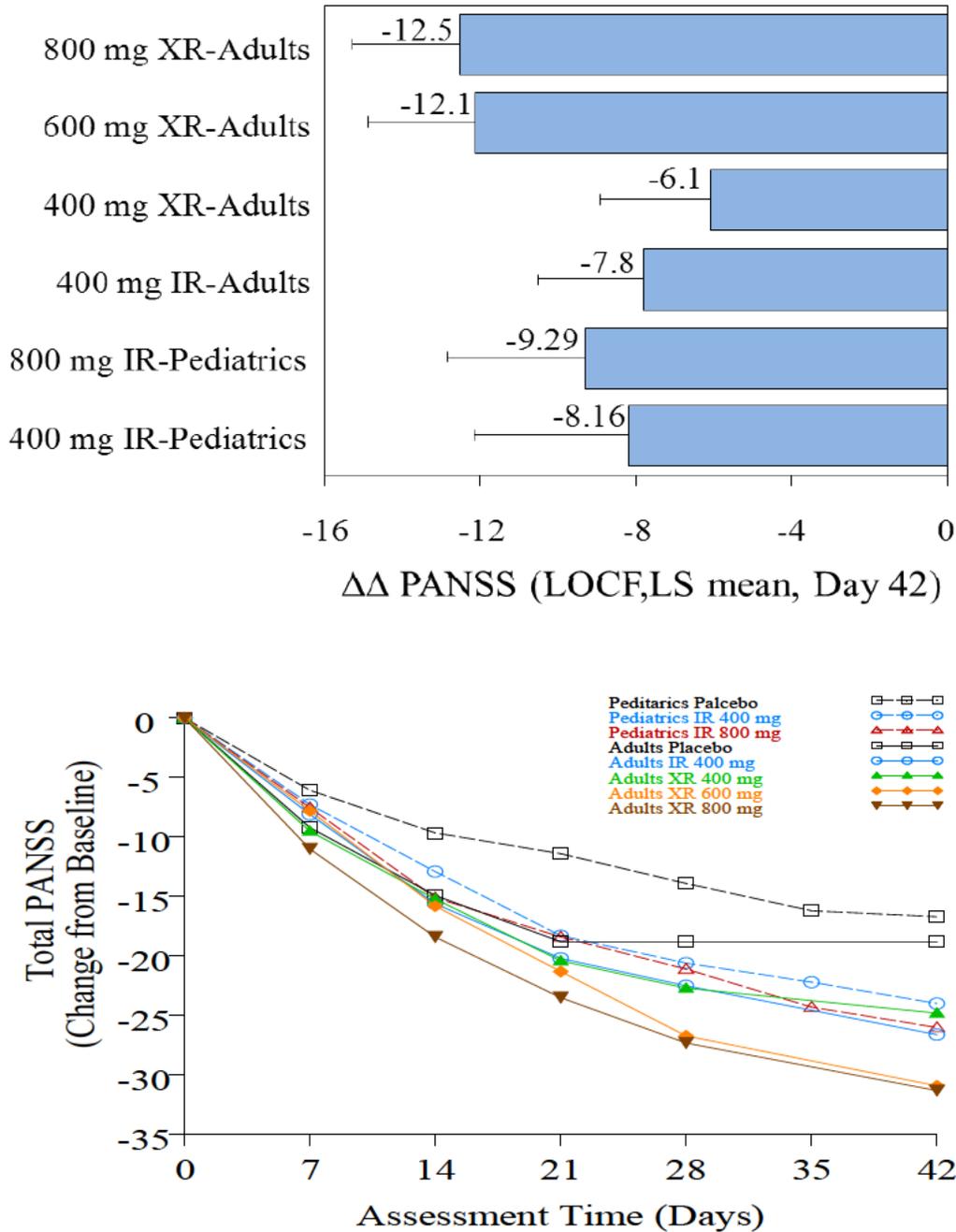
**Table 2.** Approved doses of quetiapine by indication.

Quetiapine		IR		XR	
Patient Population		Adult	Pediatrics	Adult	Pediatrics
Schizophrenia	Start	S25 mg BID	25 mg BID	300 mg/day	Not Approved
	Range	150 – 750 mg/day	400 – 800 mg/day	400 – 800 mg/day	Not Approved
Bipolar Mania	Start	50 mg BID	25 mg BID	300 mg/day	Not Approved
	Rang	400 – 800 mg/day	400 – 800 mg/day	400 – 800 mg/day	Not Approved

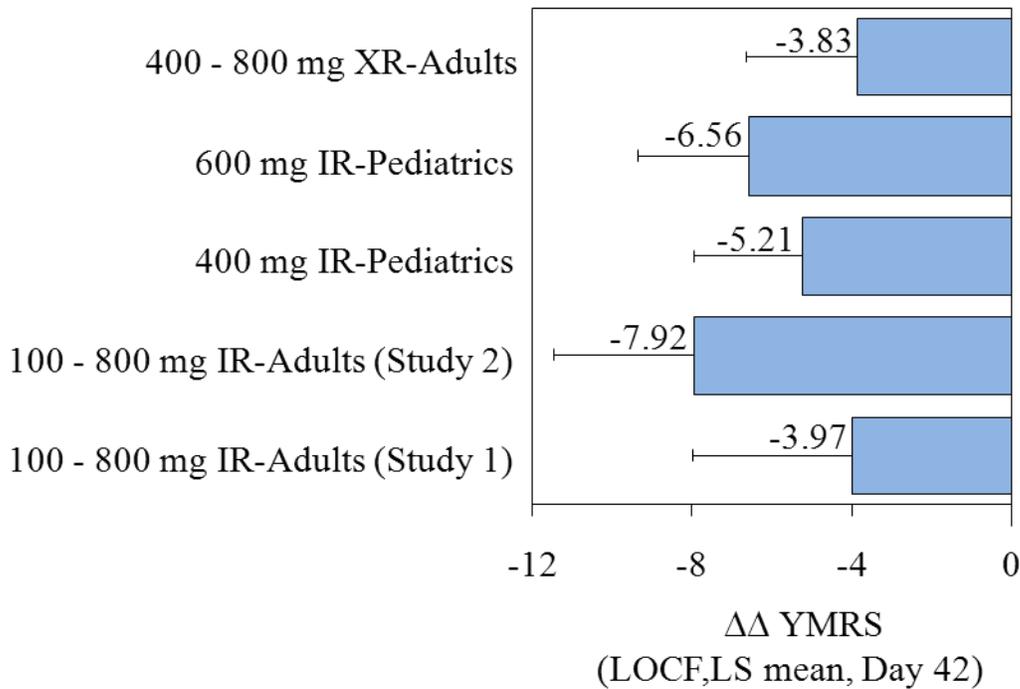
#### II. Similarity in treatment effect of QTP in adults (IR and XR) and pediatrics (IR):

1. **Schizophrenia:** QTP IR efficacy was established in three placebo-controlled clinical efficacy trials, one flexible dosing and two fixed dosing, in adults and one placebo-controlled fixed doses (400 and 800 mg/day) clinical efficacy trial in adolescents. QTP XR efficacy in adults was established in one placebo-controlled fixed dose study D144C0132 (400, 600 and 800 mg/day) which contained an IR arm (400 mg BID). Figure 1 displays mean change from baseline and placebo in total PANSS (primary endpoint) on Day 42 in placebo and treatment arms observed in clinical trials used to establish QTP IR efficacy in adolescents and QTP XR efficacy in adults. Efficacy data from clinical trials used to establish QTP IR efficacy in adults were not used since a different primary endpoint, Brief Psychiatry Rating Scale, was used in these trials. As shown in the Figure treatment effect is comparable between QTP IR and XR in adults and QTP IR in adults and adolescents.

2. **Bipolar Mania Monotherapy:** QTP IR efficacy was established in three placebo-controlled efficacy trials, one fixed doses 3-weeks trial in pediatrics 10 – 17 years of age (400 and 600 mg) and two identical 12-weeks flexible doses (100 – 800 mg) in adults. QTP XR efficacy was established in one placebo-controlled 3-weeks flexible doses (00 – 800 mg). Figure 2 displays the change form baseline and placebo in Young Mania Rating Scale (YMRS) at the end of three weeks from all trials. The effect is comparable across treatment arms.



**Figure 1.** Total PANSS following the administration of QTP IR (adults and pediatrics) and QTP XR (adults). Upper panel; change from baseline and placebo in total PANSS at Day 42 (endpoint) by treatment arm. Bars represent LS means and error bars represent standard error. Lower panel; mean change from baseline in total PANSS by assessment week and treatment arm. Adult data were derived from study D144C00132 submitted to NDA 022047(QTP XR) and pediatric data were derived from study D144C00112 submitted to sNDA 020639-S046.



**Figure 2.** Change from baseline and placebo in total YMRS at Day 21 by treatment arm. Bars represent LS means and error bars represent standard error. Adult IR data are derived from studies IL/104 (study 1) and IL/105 (study 2) submitted to sNDA 020639-S016. Pediatric data are derived from study D144C00149 submitted to sNDA 020639-

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### III. Established similar exposures between the QTP IR and XR formulations:

The similar exposures between QTP IR and XR formulations were established in study 5077IL/0097 submitted to NDA 022047. This was an open-label, steady-state, single-center, randomized, 2-period crossover study to compare the bioavailability of QTP XR 300 mg QD to QTP IR 150 mg BID in 28 patients, 18 to 62 year of age, with schizophrenia, schizoaffective disorder, or bipolar disorder. Study schema is shown below

Day	1-2 (Lead-in)	3-6	7-10
QTP	XR 300 mg	XR 300 mg QD	IR 150 mg BID
		IR 150 mg BID	XR 300 mg QD

Figure 3 depicts QTP plasma profile following the administration of IR and XR formulations in adult patient. Table 2 displays the pharmacokinetic parameters following the administration of QTP IR and XR. The geometric mean XR:IR ratio for AUC<sub>0-24</sub> was 1.04 with 90% confidence interval between 0.92 to 1.19. The XR and IR formulations can therefore be considered to have similar bioavailability with respect to overall exposure at the same daily dose.

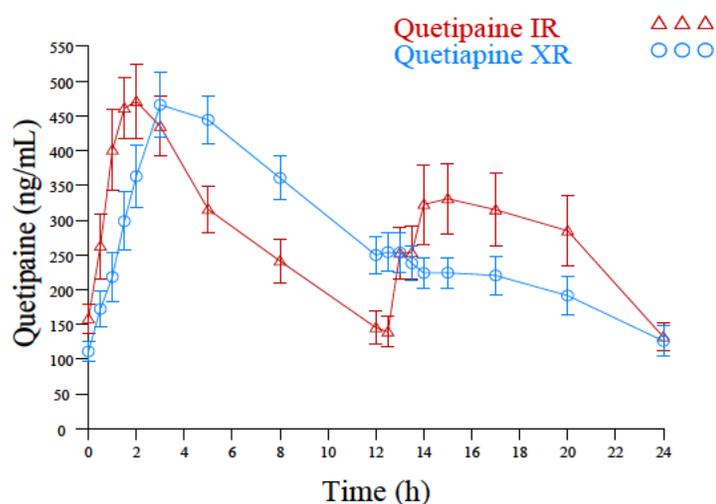
Mean C<sub>max</sub> for the XR formulation was approximately 13% lower than mean C<sub>max</sub> for the IR formulation, which is not expected to affect efficacy. There was minimal

difference between the XR and IR formulations with respect to mean  $C_{min}$ . Median  $T_{max}$  was longer for the for the XR formulation. There were no deaths, other serious adverse events, or withdrawals due to adverse events during this study.

**Table 2.** Comparison of the pharmacokinetic parameters for QTP IR (150 mg BID) and XR (300 mg QD). Value represent geometric means.

Parameter	QTP IR	QTP XR	XR/IR Ratio (90% CI)
N	24	24	24
AUC <sub>0-24</sub> (ng.h/mL)	5882	6147	1.04 (0.92,1.19)
$C_{max}$ (ng/mL)	568.1	495.3	0.87 (0.77,0.99)
$C_{min}$ (ng/mL)	96.5	95.3	1.00 (0.77,1.31)
$T_{max}$ (h)*	2.0 [0.6-0.8]	5.0[0.9-20.0]	

\* Median [Range]



**Figure 3.** QTP plasma profile following the administration of XR and IR formulation to adults patients. Points represent mean and error bars represent standard error.

The dose proportionality of QTP following the administration of QTP XR tablets was established in the dose range 100 to 800 mg in studies 5077IL/0086 and 5077IL/0118 submitted to NDA 022047. Study 0086 was an Open-label, steady-state study to evaluate dose proportionality of QTP XR over the dose range (100 mg, 200 mg, 300 mg, 600 mg, and 800 mg) and to assess the effect of food on the 200-mg and 300-mg XR tablets in patients with schizophrenia. Study 0118 was Open-label, steady-state study to evaluate the dose-unit dose-proportionality of 4 commercial-scale QTP XR tablets (50 mg, 200 mg, 300 mg, and 400 mg) and to evaluate the effect of food on the bioavailability of 50-mg and 300-mg XR tablets in patients with schizophrenia or schizoaffective disorders.

The above studies demonstrate the similarity in exposure following the administration of QTP IR and XR in the dose range 50 – 800 mg.

(b) (4)



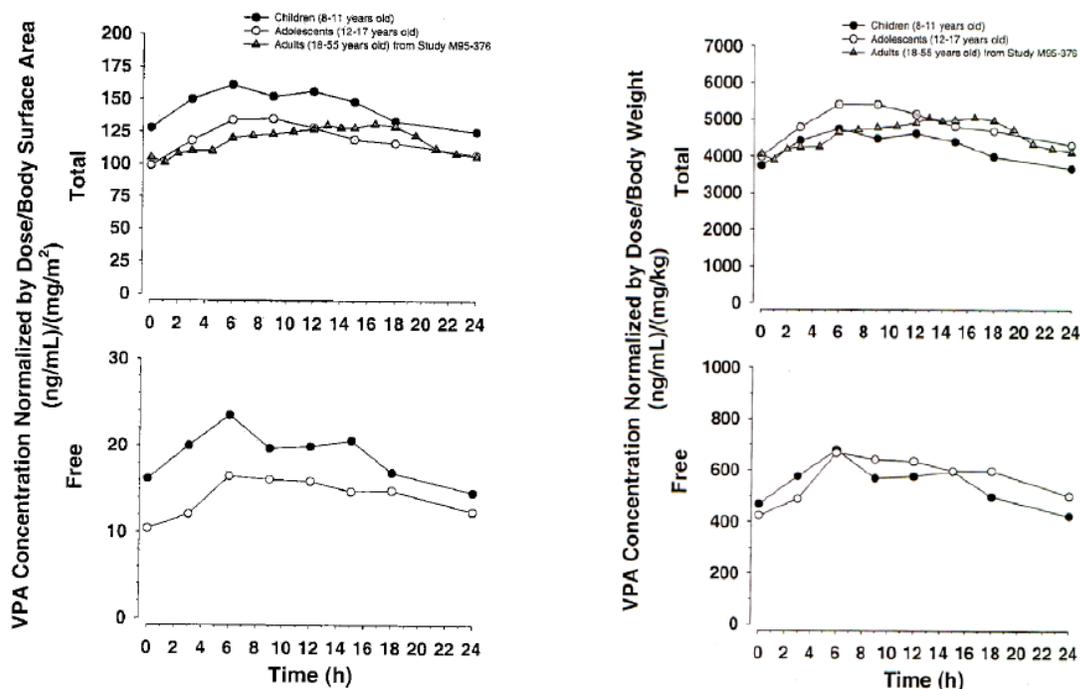
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#### IV. Similarity in pharmacokinetic behavior for XR formulations between adults and peditrics 10 – 17 years of age.

1. **Paliperidone ER:** Paliperidone is approved for the treatment of schizophrenia in adults and adolescents 12 to 17 years of age. Absorption was not associated with any covariate in a population pharmacokinetic analysis performed using data from 315 subjects, 166 peditrics 10-7 years of age and 153 adults, from 2 adolescent (one phase I and one phase III) and 3 phase I adult trials. The pharmacokinetics of paliperidone in plasma was best described by an open, 2-compartment disposition model with linear elimination from the central compartment. The absorption was modeled as a sequential zero- and first-order input process. No formulation related parameter was associated with age.

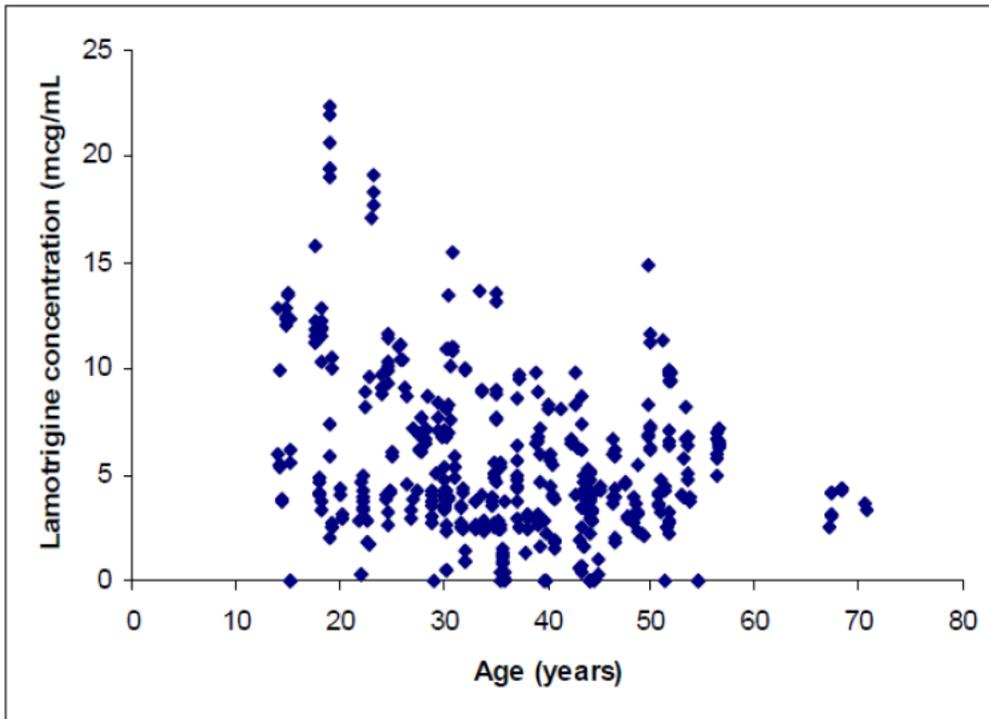
2. **Divalproex sodium ER:** Divalproex sodium ER is indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years. The efficacy of divalproex sodium ER could not be established for the indications of either migraine (12- 17 years) or bipolar disorders (10 to 17 years) in the efficacy trials. Per the approved divalproex sodium label on 10/15/2009 “The valproate pharmacokinetic profile following administration of divalproex sodium ER was characterized in a multiple-dose, non-fasting, open label, multi-center study in children and adolescents. divalproex sodium ER once daily doses ranged from 250-1750 mg. Once daily administration of divalproex sodium ER in pediatric patients (10-17 years) produced plasma VPA concentration-time profiles similar to those that have been observed in adults.” (Figure 5).



**Figure 5.** Pharmacokinetics of valproic acid following the administration of Depakote ER in children (8-11 years), adolescents (12-17 years) and adults (18-55 years). Figure adapted

from the clinical pharmacology review of NDA 21168-S007 performed by Drs. Yasuda and Uppoor.

3. **Lamotrigine XR:** Lamotrigine IR and XR formulations are approved for the treatment for epilepsy in patients 13 years of age and older. The approved doses are the same for both formulation and conversion from IR to XR should be based on matching the total daily dosing. According to the clinical pharmacology review of NDA 22115 dated on 09/06/2007, the population analysis of the pivotal clinical study showed that age did not affect lamotrigine plasma concentration (Figure 6). It should be noted that pediatric data was obtained from 7 children on treatment based on sparse sampling, 4 – 6 samples per subject. In addition, IR and XR formulations were shown to have similar AUC (XR/IR ratio: 0.9 with 90%CI of 0.84 to 0.98) even though  $C_{max}$  was slightly lower for XR (XR/IR ratio: 0.82 with 90% CI of 0.76 to 0.90).



**Figure 6.** Effect of age on lamotrigine plasma concentrations. Adapted from clinical pharmacology review of NDA 22115 dated on 09/06/2007.

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No. The review team has the following comments [REDACTED]

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