October 25, 2010

The Honorable Margaret A. Hamburg
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via: E-mail margaret.hamburg@fda.hhs.gov

Dear Commissioner Hamburg:

The Project On Government Oversight is an independent, nonprofit organization that provides oversight of the federal government. We take a keen interest in the U.S. Food and Drug Administration (FDA), which receives around $4 billion a year in federal taxpayer dollars to regulate almost twenty-five percent of the U.S. economy.

We would like to bring to your attention a potentially dangerous interaction of the drugs Seroquel (quetiapine) and methadone that may be putting veterans at risk. According to news accounts, these drugs are now widely used in combination to treat veterans with Post-Traumatic Stress Disorder (PTSD). However, a study published in 2007, and funded by Seroquel’s maker, AstraZeneca, found that Seroquel significantly increases plasma levels of methadone. This may increase the risk of a methadone overdose.

Further, between 2002 and July 2010, the FDA’s Adverse Event Reporting System (AERS) received over eighty reports of patients who overdosed and often died while taking Seroquel in combination with methadone. As I’m sure you are aware, AERS reports are known to underestimate the true number of drug adverse events, so POGO is alarmed that so many reports have been filed with the FDA on Seroquel and methadone interactions.

However, despite the known interaction effect, the FDA-approved labels for Seroquel and methadone do not note the study from 2007, and the labels do not discuss this interaction in the warning section. In the interest of patients, and especially veterans, we ask that you make changes to both labels to note this drug interaction. Further, we ask that you immediately issue an alert to inform patients and prescribers.
BACKGROUND

The dangers of Seroquel and methadone were first reported in a study published in 2007 in the *Journal of Clinical Psychopharmacology.*¹ This study found that Seroquel significantly increases blood plasma levels of methadone. In one patient, Seroquel led to an 85 percent increase in blood plasma levels of methadone. The study found wide variability across patients, which the authors argue may be due to differences in genetic subpopulations.

Yet, prescriptions of Seroquel and methadone are at an all time high for veterans. An investigation by the *Military Times* found that military spending on Seroquel almost quadrupled between 2001 and 2009.²

Many of these veterans are also taking methadone for pain relief and to control anxiety caused by PTSD. The *Military Times* found that methadone overdose has caused at least sixty death deaths in the military, more than any other drug—legal or illegal.³

A separate investigation by the *Associated Press* noted that military expenditures on Seroquel have jumped sevenfold since the beginning of the war in Afghanistan.⁴ The military spent $8.6 million on Seroquel last year alone.⁵ Physicians said that they are prescribing it to provide relief from nightmares and anxiety caused by PTSD. The *Associated Press* also discovered that Seroquel has become the Department of Veterans Affairs’ (VA) second biggest drug expenditure since 2007. Last year the VA spent $125 million on Seroquel compared to $14.4 million in 2001.⁶

In the case of one soldier, Andrew White, the *Associated Press* reported that the interaction of Seroquel and methadone may have been deadly.⁷ To treat his PTSD, he was prescribed Seroquel, methadone, and Paxil. Mr. White’s autopsy report stated, “The narcotic analgesic methadone was present in the blood at a concentration that can cause fatal respiratory depression in those who do not have adequate tolerance to opioid medications.”

Again, POGO urges FDA to improve the labels of Seroquel and methadone to note the 2007 study in the *Journal of Clinical Psychopharmacology.* Further, we ask FDA to issue an alert to inform patients and prescribers. We also have concerns about the quality of the data in the AERS.

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⁵ Perrone, “Questions Loom.”
⁶ Perrone, “Questions Loom.”
⁷ Perrone, “Questions Loom.”
database and how the FDA uses this information to monitor for adverse drug events. To help answer our concerns, we ask that FDA provide someone to brief our staff.

We have attached a copy of the 2007 study in the *Journal of Clinical Psychopharmacology* and copies of the FDA’s AERS reports noting an adverse reaction to Seroquel and methadone.

I appreciate your review of this letter and the attached documents. If you have any questions, please do not hesitate to contact Paul Thacker at (202) 347-1122 or thacker@pogo.org.

Sincerely,

Danielle Brian  
Executive Director

Enclosures: 2

cc:  Senator Carl Levin  
Chairman, Senate Armed Services Committee  

Senator John McCain  
Ranking Member, Senate Armed Services Committee  

Senator Daniel K. Akaka  
Chairman, Senate Veterans’ Affairs Committee  

Senator Richard Burr  
Ranking Member, Senate Veterans’ Affairs Committee  

The Honorable Eric K. Shinseki  
Secretary  
Department of Veterans Affairs  

George Peach Taylor Jr., M.D., MPH  
Acting Assistant Secretary of Defense for Health Affairs  
Department of Defense
Study published in 2007 in the *Journal of Clinical Psychopharmacology*
Increased (R)-Methadone Plasma Concentrations by Quetiapine in Cytochrome P450s and ABCB1 Genotyped Patients

Claude Uehlinger, MD,* Sèverine Crettol,† Philippe Chassot,* Murielle Brocard,† Liliane Koeb,† Marlyse Brawand-Amy,† and Chin B. Eap, PhD†

Abstract: Steady-state plasma concentrations of (R)- (ie, the active form), (S)-, and (R,S)-methadone were measured in 14 addict patients in methadone maintenance treatment, before and after introduction of quetiapine, administered at a mean dosage of 138 mg/d (SD, 87 mg/d; median, 125 mg/d; range, 50–300 mg/d) during a mean period of 30 days (SD, 8 days; median, 30 days; range, 20–48 days). Eleven patients were genotyped as being CYP2D6 extensive metabolizers (EMs) and 3 patients as poor metabolizers. Eleven patients had the ABCB1 3435 CT or CC genotypes, and 3 patients had the ABCB1 3435 TT genotype, the latter genotype being associated with lower P-glycoprotein activity. Quetiapine significantly increases (R)-methadone concentration-dose ratios in the whole group [increase for (R)-methadone: mean, +21%; SD, +28%; median, +13%; range, −23% to +85%; P = 0.026], but not for (S)-methadone: mean, +23%; SD, +43%; median, +6%; range, −30% to +115%; P = 0.12] or for (R,S)-methadone: mean, +21%; SD, +34%; median, +9%; range, −21% to +95%; P = 0.064). The mean increases of (R)-methadone concentration-dose ratios were of 7%, 21%, and 30% in the CYP2D6 poor metabolizers, heterozygous EMs, and homozygous EMs, respectively, whereas they were of 3%, 23%, and 33% in the subjects with the ABCB1 3435 TT, CT, and CC genotypes, respectively. Thus, quetiapine increases the plasma concentrations of (R)-methadone, possibly in part by an interaction with CYP2D6 and/or with the P-glycoprotein transporter system. No signs of overmedication caused by increased methadone plasma concentrations were noticed by the staff or reported by the patients.


Methodadone is metabolized by several isoforms of the cytochrome P450 (CYP) family, mainly CYP3A4 and CYP2B6, and to a lesser extent by CYP2D6.1–5 Psychiatric comorbidity is highly prevalent among drug abusers,6 and antidepressants and/or antipsychotics are commonly prescribed to patients in methadone maintenance treatment (MMT). We conducted several studies examining the in vivo influence of coadministrations of psychotropic drugs on the plasma levels of methadone in patients in MMT. We have thus previously shown that fluoxetine and fluvoxamine, 2 antidepressants of the selective serotonin reuptake inhibitor class, significantly increase the concentrations of methadone.7,8 Interestingly, whereas fluvoxamine increased the concentrations of both enantiomers of methadone [ie, (R)-methadone or levomethadone, the active enantiomer, and (S)-methadone or dextromethadone, the inactive enantiomer], only (R)-methadone concentrations were increased by the addition of fluoxetine.9 This suggested that CYP2D6, which is strongly inhibited by fluoxetine, is preferentially involved in the metabolism of the (R)-enantiomer, whereas CYP3A4, which is inhibited by fluvoxamine,9 does not display any stereoselective activity toward methadone.9,10 A stereoselectivity of CYP2D6 toward (R)-methadone was also suggested by a subsequent study measuring the in vivo influence of paroxetine, another strong inhibitor of CYP2D6.9 Thus, whereas in 8 patients in MMT genotyped as being extensive metabolizers (EMs) of CYP2D6, paroxetine increased the plasma concentrations of both enantiomers of methadone, possibly by a strong inhibition of CYP2D6 and a mild inhibition of CYP3A4, in the 2 patients genotyped as being CYP2D6 poor metabolizers (PMs), (S)-methadone, but not (R)-methadone, was increased by paroxetine administration.9 Quetiapine is an atypical antipsychotic drug that is metabolized mainly by CYP3A4, but a small contribution of CYP2D6, for the 7-hydroxylation pathway, can be expected.11 Quetiapine and several of its metabolites have no effect on the in vitro activity of CYP1A2, CYP2C9, CYP2C9, and CYP3A4 at clinically relevant concentrations.12 (AstraZeneca, data in file). However, the inhibitory potential toward CYP enzymes has not been tested for all metabolites of quetiapine, and the inhibitory effect of quetiapine and/or of its metabolites toward CYP2B6 has not been tested either. In addition, both quetiapine and methadone are substrates of the efflux transporter permeability glycoprotein (PGP) encoded by the ABCB1 gene,13–15 and interactions through this transporter system are also possible. We therefore examined whether the prescription of quetiapine to MMT patients could result in modified methadone plasma concentrations.

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Received August 25, 2006; accepted after revision February 9, 2007.

This work has been supported, in part, by a grant from AstraZeneca. Address correspondence and reprint requests to Chin B. Eap, PhD, Hôpital de Cery, CH 1008 Prilly-Lausanne, Switzerland. E-mail: Chin.Eap@chuv.ch.

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ISSN: 0271-7144/07/2703-0273
DOI: 10.1097/JCP.0b013e3180592ad2

Journal of Clinical Psychopharmacology • Volume 27, Number 3, June 2007

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As any interaction with methadone metabolism and/or transport by quetiapine, through an inhibition of CYP enzymes and/or PGP activities, is dependent on the CYP and ABCB1 genotypes, patients were genotyped for CYP3A5, CYP2B6, CYP2D6, and ABCB1 (no genotyping was done on CYP3A4 because genotyping this isoyme poorly reflects its activity).

PATIENTS AND METHODS

This study was performed in Fribourg, and the corresponding ethics committee approved the protocol of the study (including the genetic analyses). The study was proposed to male and female addicts patients (>18 and <65 years) in methadone maintenance therapy who were about to start an antipsychotic therapy with quetiapine. Patients had to be treated with methadone for at least 1 month, with an unchanged dose for at least 1 week. Exclusion criteria included a known sensitivity to quetiapine, pregnant or breastfeeding women (a pregnancy test was carried out in all women of child-bearing age), introduction of a new comedication for less than 1 week before the inclusion, or change of the dose of the comedication within the last week before inclusion. Doses of quetiapine (immediate-release form, twice a day) were variable and chosen by the physician in charge of the patient, depending on the clinical state of the patients and independently from the study. Patients had to give their written informed consent to participate in the study. Twenty patients were included, but 5 subjects dropped out before the second blood sampling. A sixth patient was removed from further data analysis as the blood sample drawn after quetiapine treatment revealed undetectable quetiapine plasma levels, suggesting noncompliance. For each patient, the first blood sample was taken before the introduction of quetiapine, at least 5 days after any change of methadone dose (doses with methadone dose kept unchanged: mean, 168 days; SD, 195 days; median, 81 days; range, 6-604 days) and at least 1 week after any changes of comedications. The second blood sample was taken after at least a 7-day treatment with quetiapine. Blood samples were taken at trough, just before the next methadone intake.

One patient had no comedications, and the 13 remaining patients were taking other drugs, none of which, with 1 exception, were known to be inducers or strong inhibitors of CYP enzymes [bromazepam (1 patient), (R,S)-citalopram (5 patients), escitalopram (1 patient), clonazepam (2 patients), clorazepate (1 patient), olanzapine (1 patient), trimipramine (1 patient), zolpidem (4 patients), and zopiclone (10 patients)]. One patient had paroxetine (20 mg/d) as comedication, a strong CYP2D6 inhibitor, but this treatment was maintained at constant dosage during the study. In all but 2 patients, the comedications were kept constant between the 2 blood samplings. In 1 patient, between the 2 blood samplings, citalopram dose was increased from 20 to 60 mg/d, zopiclone (7.5 mg/d) was withdrawn, and biperiden (4 mg/d) and zolpidem (10 mg/d) were introduced. In another patient, (R,S)-citalopram (40 mg/d) was replaced by escitalopram (20 mg/d), zolpidem (30 mg/d) was interrupted, and bromazepam (30 mg/d) and chloral hydrate (500 mg/d) were introduced. As none of these changes of comedications were expected to influence methadone plasma levels, and as similar results were obtained when removing the data of these 2 patients (data not shown), their data were kept for the final analysis. Two of the 14 patients had methadone doses modified between the 2 blood samplings, and methadone plasma levels—dose ratios were therefore used for statistical calculations for all patients. Urea and creatinine levels were within normal values in all patients, whereas hepatic functions were either normal or slightly disturbed (values of γ-glutamyltransferase, alanine aminotransferase, and/or aspartate aminotransferase less than 3-fold the reference range) in 13 patients and moderately disturbed in 1 patient (values <6-fold the reference range).

(R)- and (S)-methadone plasma concentrations were measured by high-performance liquid chromatography—mass spectrometry as previously described.2 The concentrations of quetiapine were determined using a high-performance liquid chromatography column (analytical column: EC 125/2 Nucleosil 100-5 C18, 5-μm silica gel, 125 × 2 mm; Astec, Basel, Switzerland) with a mass spectrometer detector (HP 1100 series; Agilent Technologies, Palo Alto, Calif) after a liquid-liquid extraction step. The LC conditions were as follows: mobile phase, 35% tetrahydrofuran—65% 4 mmol/L NH4NO3—1.5% methanol; flow rate, 0.3 mL/min. Analyses were performed in the selected-ion monitoring mode for the ions at m/z 384.2. The limit of quantification was 0.4 ng/mL. Intraday and interday coefficients of variation determined at 3 concentrations ranged from 0.9% to 1.8% (unpublished method, detailed method available on request).

Genotyping of CYP2D6 was performed by real-time polymerase chain reaction with the use of S' nucleic acid allelic discrimination assays (alleles *3, *4, *6; ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland), and as previously described for the allele *5 and *XN, Genotyping of CYP3A4 (allele 2). Genotyping of CYP3A5 (alleles *2, *4, *5, *6, *7, *9) and ABCB1 (3435C>T) was performed as previously described. The Wilcoxon matched paired test was used to compare the concentrations of methadone measured before and after introduction of quetiapine, and the Mann-Whitney U test was used to compare different quetiapine and methadone plasma levels between different CYP or ABCB1 genotypes (Statistica Release 4.5, Statsoft; Loll & Nielsen, Hamburg, Germany). A P value lower than 0.05 was considered as statistically significant. In the original protocol, it was planned to include 15 patients. Based on previously published mean and SDs of methadone plasma concentrations, a sample size of 15 would achieve 80% power to detect a difference of 32% in the mean concentration of methadone with a significance level (α) of 0.05.

RESULTS

Fourteen patients were finally included in the study (all were white and smokers; 11 men). The mean age of the patients was 34 years (SD, 8 years; median, 35 years; range, 23-46 years), and the mean weight was 71 kg (SD, 14 kg; median, 72 kg; range, 44-96 kg). The mean duration of
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The P values for changes of (R)-, (S)-, and (R,S)-methadone concentration-dose ratios after quetiapine administration are given.
EM indicates extensive metabolizer; IM, intermediate metabolizer; PH, poor metabolizer.
methadone treatment at inclusion was 1332 days (SD, 1084 days; median, 1244 days; range, 162–3325 days). The mean dose of methadone was 121 mg/d (SD, 67 mg/d; median, 130 mg/d; range, 12–240 mg/d) at the first blood sampling (before quetiapine) and was 119 mg/d (SD, 68 mg/d; mean, 130 mg/d; range, 12–240 mg/d) at the second blood sampling. The mean quetiapine dose was 138 mg/d (SD, 87 mg/d; mean, 125 mg/d; range, 50–300 mg/d), which was administered for a mean duration of 30 days (SD, 8 days; mean, 30 days; range, 20–48 days). No quetiapine could be detected in the blood of patients before the introduction of quetiapine. At the second blood sampling, the mean quetiapine plasma level was 51 ng/mL (SD, 57 ng/mL; mean, 32 ng/mL; range, 3–183 ng/mL; Table 1).

All patients were found to be CYP3A5 PMs, with the *5/*3 genotype, a high prevalence of this allele confirming previous studies in whites. Two patients were found to be CYP2B6 *6/*6, a genotype found to be associated with decreased CYP2B6 activity and higher (S)-methadone plasma levels. Three patients were found to be CYP2D6 PMs (*5/*4, 1 patient; *4/*4, 2 patients) and 1 to be EMs, either heterozygous (intermediate metabolizers or IMs, *1/*4 or *1/*3, 7 patients) or homozygous (*1/*1, 4 patients). No patient was found to be CYP2D6 ultrarapid metabolizer.

Three patients were found to have the ABCB1 3435 TT genotype, which is generally associated with lower PGP activity due to reduced mRNA stability. 8 and 3 patients were found to have the ABCB1 3435 CT and CC genotypes, respectively. Quetiapine plasma levels—dose ratios were not significantly different between CYP2D6, CYP2B6, and ABCB1 genotypes (data not shown). Likewise, methadone plasma levels—dose ratios were not significantly different between ABCB1 and CYP2D6 genotypes (data not shown).

On the other hand, (S)-methadone (P = 0.034), but not (R)-methadone (P = 0.10), plasma levels—dose ratios were significantly higher in the 2 patients with the CYP2B6 *6/*6 genotype as compared with the 9 patients with 0 or 1 *6 allele [mean (S)-methadone: 2.54 vs. 1.38 ng/mL × mg], which confirms a previous study showing a strong influence of this genotype on (S)-methadone plasma levels.

A significant increase of methadone concentration—dose ratios was measured after introduction of quetiapine, in the whole group for (R)-methadone [increase for (R)-methadone: mean, +21%; SD, +28%; median, +13%; range, −23% to +85%; P = 0.026] but not for (S)-methadone (mean, +23%; SD, +43%; median, +6%; range, −30% to +115%; P = 0.120) or for (R,S)-methadone (mean, +21%; SD, +34%; median, +9%; range, −21% to +95%; P = 0.064).

No significant correlations could be observed between the increases of the (R), (S), and (R,S)-methadone concentration—dose ratios measured after the introduction of quetiapine with quetiapine plasma levels (P = 0.71, 0.96, and 0.92, respectively). Although the changes of the methadone concentration—dose ratios observed after quetiapine administration were not significantly different between the CYP2B6, CYP2D6, and ABCB1 genotypes, possibly because of the low number of patients of each genotype, interestingly, the mean modifications of the (R)-methadone concentration—dose ratios were of 7%, 21%, and 30% in the CYP2D6 PMs, IMs, and EMs, respectively, whereas they were of 3%, 23%, and 33% in the subjects with the ABCB1 3435 TT, CT, and CC genotypes, respectively. Table 1 lists the mean methadone concentration—dose ratios measured before and after the introduction of quetiapine, with the CYP2D6, CYP2B6, and ABCB1 genotypes.

### DISCUSSION

The present result shows a weak (21%) but significant increase of the concentration—dose ratios of (R)-methadone, but not (S)-methadone, in patients in MMT after quetiapine administration. The absence of a significant effect on the (S)-enantiomer plasma levels could be due to the low number of patients included and to an insufficient power to detect a small change. Based on in vitro data, it is not expected that this interaction is due to an inhibition by quetiapine of the CYP isozymes implicated in methadone metabolism. This is also supported by the lack of correlation between quetiapine plasma levels and increase of methadone concentration—dose ratios observed in this study. One can formulate the hypothesis that one or several quetiapine metabolite(s), which are produced in vivo and which were not included in the in vitro interaction study performed by AstraZeneca (AstraZeneca, data in file), are responsible for this interaction. Alternative or additional mechanisms by which quetiapine and/or quetiapine metabolites could interact with methadone pharmacokinetics could be an inhibitory effect toward CYP2B6, which has not been tested in the above-mentioned study (AstraZeneca, data in file) and/or an inhibitory effect toward the PGP transporter system.

With regard to CYP2B6, in vitro and in vivo studies showed a stereoselectivity of this isozyme toward the (S)-enantiomer, which is in apparent contradiction with the idea of an interaction with this isozyme to explain an increase of (R)-methadone concentration—dose ratios. With regard to the PGP transporter, a study using knockout mice suggested that it could display a stereoselectivity toward the (S)-enantiomer, such a stereoselectivity being not confirmed in vivo. Interestingly, although no statistically significant differences were found between the different CYP and ABCB1 genotypes, one can mention that the lowest increases of (R)-methadone concentrations were measured in the CYP2D6 PMs (7%) and in the patients with the ABCB1 3435 TT genotype (3%, not the same patients). Accordingly, higher increases were measured in the CYP2D6 IMs (21%) and in the patients with the ABCB1 3435 CT genotype (23%), whereas the highest increases were measured in the CYP2D6 EMs (30%) and in the patients with the ABCB1 3435 CC genotype (33%). This result is in agreement with a previous study showing an increase of (R)-methadone plasma levels in the CYP2D6 EMs but not in PMs after the administration of paroxetine, a strong CYP2D6 inhibitor, and is in agreement with the hypothesis that an inhibition of methadone metabolism and/or transport can be best observed in subjects with the highest baseline metabolic and/or transport activity. As CYP2D6 is not known to be expressed in the gut, a possible inhibition of CYP2B6 by quetiapine presumably occurs in the liver. On
the other hand, it is not known whether a possible inhibition of PGP by quetiapine occurs in the gut and/or in the liver. In addition, the present results do not allow to draw any conclusions on the possible interactions of quetiapine and/or of quetiapine’s metabolites with CYP3A4, the other main CYP isoform with CYP2B6 implicated in methadone metabolism.

At least with a low mean daily dose of 138 mg of quetiapine administered during the present study, the mean 21% increase of the plasma concentration of (R)-methadone is weak and smaller than changes observed after the administration of other psychotropic drugs such as paroxetine, fluvoxamine, and fluoxetine and is unlikely to be of clinical importance. Thus, it is not expected that such a weak increase would result in clinically significant effects in relation to respiratory depression, due to the high tolerance of patients in maintenance treatment to the opioid effect of methadone. In the present study, no signs of overmedication or intoxication were noticed by the staff or reported by the patients despite the fact that an increase of (R)-methadone plasma levels—dose ratios up to 85% was measured in one patient. On the other hand, as the elimination half-life of quetiapine is short, that is, approximately 7 hours, and as opioid withdrawal symptoms have been described after a sudden stop of fluvoxamine, such effects might theoretically also occur when quetiapine treatment is abruptly interrupted. In the present study, as quetiapine treatment continued after the second blood sampling, no such side effects were noticed.

Very recent studies show that methadone can prolong the QT interval and cause torsades de pointes, the use of high methadone doses being a risk factor. Rare cases of QT-interval prolongation have also been shown with quetiapine. As the present study was conducted before the cases of torsades de pointes under methadone were published, no electrocardiography was performed, and we can therefore not draw any conclusions regarding this point. This must, however, clearly be examined in future studies, along with the use of higher quetiapine doses. From a practical point of view, considering the strong increase of methadone plasma levels in some patients after the introduction of various combinations, such as quetiapine, fluoroxamine, fluoxetine, or paroxetine, and considering the apparent unpredictability of this interaction (i.e., which individuals would have an increase of methadone plasma levels and to what extent), therapeutic drug monitoring of the enantiomers of methadone, performed before and after the administrations of specific combinations known, likely or suspected to interact with methadone pharmacokinetics, can be a helpful tool in the clinical management of patients in MMT. The present study, as well as a previous study with paroxetine suggesting that the genetic status of the patients could strongly influence the interactions of comedictions with methadone, clearly warrant future studies with larger numbers of genotyped patients, to confirm these results. In the future, this could hopefully allow to better predict the potential interactions occurring when administering comedictions to patients in MMT.

ACKNOWLEDGMENTS

The authors thank Mrs V. Sari and Mrs K. Powell Golay for editorial assistance and Mrs J. Rosselet, Mrs M. Gobin, and Mrs E. Ponce for bibliographic help.

REFERENCES


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Adverse Events Reporting System (AERS) reports on seroquel/methadone combination overdoses
FDA - Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 11/07/2015 Number: 4009510-1 Report Type: Expedited 15-DeCompany Report #2002AD05570

Outcome
Death

Report Source
Foreign

Product
Leukemia

Role
Manufacturer
PS

Route
Oral

Dose
500 mg QD PO

Duration
24-Aug-2010 10:39 AM

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