



April 15, 2011

Danielle Brian, Executive Director
Paul Thacker, Investigator
Project on Government Oversight
1100 G St., NW
Suite 900
Washington, DC 20005-3806

Dear Ms. Brian and Mr. Thacker,

Thank you for your letter of October 25, 2010, regarding a potentially dangerous drug interaction when the drugs quetiapine (Seroquel®) and methadone are used concurrently. You note that “according to news accounts, these drugs are now widely used in combination to treat veterans with Post-Traumatic Stress Disorder (PTSD).” In that context you refer to a 2007 study, which found that concomitant use of quetiapine and methadone might contribute to elevations of methadone.

The Food and Drug Administration (FDA or the Agency) takes very seriously any possibility that an approved drug product or drugs used in combination may place any American citizen at unacceptable risk. To that end, we have carefully examined the issues and concerns you raise. Our evaluation has included lengthy and extensive review by FDA medical officers and scientists within the Center for Drug Evaluation and Research (CDER), representing the Division of Pharmacovigilance I (DPV I) within the Office of Surveillance and Epidemiology (OSE), the Division of Psychiatry Products (DPP) within the Office of New Drugs (OND), and the Office of Clinical Pharmacology.

The above referenced FDA reviews included analyses of the clinical pharmacology of both quetiapine and methadone, as well as the known effects and interactions of these drugs in human physiology; a detailed search of the FDA Adverse Event Reporting System (AERS) database to cull out unique cases in which quetiapine and methadone used in combination were either probably or possibly associated with significant adverse events or death; a search of the open scientific literature to identify any other studies or reports involving a quetiapine/methadone interaction that might confer unacceptable risk, and, specifically, an analysis of the 2007 study you reference (“Increased (R)-Methadone Plasma Concentration by Quetiapine in Cytochrome P450s and ABCB1 Genotyped Patients,” *Journal of Clinical Psychopharmacology*, Volume 27, Number 3, June 2007).

After assessment of our evaluations, we believe that a potentially dangerous interaction involving quetiapine and methadone is unlikely, and, therefore, no further Agency action is indicated regarding either a revision in labeling that would include new warnings or cautions, or targeted public and professional communications efforts.

In supporting this conclusion, FDA scientists noted several key points:

- The metabolic properties and pharmacokinetics (chemical and physical processes involved in drug effects in the body) of quetiapine and methadone suggest no scientific basis for anticipating

- that their use in combination will lead to elevated levels of methadone in the bloodstream or enhanced methadone effects through another mechanism.
- The AERS database was searched to identify unique cases that might reliably support conclusions regarding a quetiapine/methadone interaction risk.
 - Searching AERS for drug interaction reports with the reported outcome of death, and where quetiapine or methadone were listed as either the suspect or concomitant drug, retrieved 182 reports. Of these, however, 165 were excluded for the following reasons: duplicate report (96), an obvious alternative cause of death (62), insufficient information to warrant further evaluation (6), or no use of methadone (1); leaving 17 unique cases for review.
 - Our reviewers also retrieved the 224 AERS reports included with your letter. Of these, 206 were excluded for the following reasons: no indication the patient had taken methadone (170), an obvious alternative cause of the death or non-fatal adverse event (20), or duplicate report (16). Of the 18 remaining unique cases, 9 were already included in our own AERS search (the 17 cases referenced above). The other 9 cases (8 nonfatal and 1 fatal) were included in our review.
 - These two approaches to culling out unique AERS reports of interest offered 26 cases for review, including 18 fatal and 8 nonfatal cases. None of these cases identified PTSD as the indication for which this drug combination was being used. (While such information would be useful, it is also of note that neither quetiapine or methadone is indicated for the treatment of PTSD, which means that using this drug combination for the treatment of PTSD would constitute an unapproved (“off label”) use of either drug.)
 - The 26 case reports of interest suffer from many of the challenges often found with spontaneous reporting, including a lack of adequate information, which prevented an in-depth analysis of the potential drug interaction. Additionally, several cases reported the use of other medications that either had the potential to interact with quetiapine and/or methadone or were a drug of abuse, which may have contributed to the adverse event. Despite this, we applied a causality assessment tool widely used in drug adverse event assessment (the WHO-UMC causality criteria). In this assessment, one case was considered probable (unlikely to be attributed to disease or other drugs), 16 possible (could also be explained by disease or other drugs), 2 unlikely, and 7 unclassifiable.
 - The most that can be concluded from the single “probable” and relatively few “possible” cases is that a potential quetiapine-methadone interaction cannot be ruled out.

A search of the scientific literature for relevant studies or reports yielded only the Uehlinger, et al. report that you reference in your letter, so there is no wider body of data to consult for comparison. The Uehlinger study has a number of methodological flaws, including a very small study population (14 individuals), poor control of sampling times, drug doses, and concurrent medications beyond quetiapine and methadone, and highly variable methadone exposures. Our reviewers also noted that the greatest measured increase of methadone in the bloodstream in one study participant was still within the exposure range observed even before adding quetiapine. In general, the study noted only modest increases in methadone levels, and the authors themselves acknowledge that such modest increases would not likely have any clinical significance. They also acknowledge that there were no signs of overmedication or intoxication in this study, even in the patient who had the greatest measured increase in methadone level. With these factors in mind, and on the basis of this one small study, our reviewers do not feel that any firm conclusions about a quetiapine/methadone drug-drug interaction are warranted.

In addition to the points discussed above, we reviewed data available to us through the Federal Partners' Collaboration (FPC). Our review of the preliminary data received through this partnership does not support an interaction between quetiapine and methadone that is associated with all-cause death. Specifically, the Army does not have evidence of a large number of soldiers concurrently exposed to quetiapine and methadone, nor does the Army have evidence of using this drug combination for treatment of PTSD.

At this point, there is agreement within CDER that an interaction between quetiapine and methadone that confers unreasonable risks to patients is exceedingly unlikely and, therefore, no further action is indicated regarding the labeling for these products or for related communication initiatives.

A challenging aspect of drug regulation and drug product oversight is the fact that all medicines carry risks as well as benefits. It is rarely possible to predict beyond any doubt which individuals may have increased sensitivity to a medicine or will experience side effects from a particular drug. FDA makes every effort to monitor products we regulate for adverse event signals, and to widely communicate reliable information regarding drug-related risks, including in product labels, boxed warnings, Medication Guides for consumers, MedWatch Safety Alerts, Consumer Updates, Drug Safety Communications, "Dear Health Care Provider" letters, and press releases.

Thank you for contacting us regarding this important matter. If we can answer any further questions, please be in touch.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written in a cursive style.

Janet Woodcock, MD

Director

Center for Drug Evaluation and Research