

NOTE TO REVIEWERS
Meeting Request
NDA 20-592, Zyprexa (olanzapine) – Proposed Labeling Revision

INTRODUCTION

The intent of this meeting is to discuss proposed labeling based on a review of integrated safety data from seven clinical studies of olanzapine in elderly patients with dementia.

Five of the seven studies included in this safety review were designed and conducted to support a clinical development plan for the treatment of psychosis associated with dementia. One study was designed and conducted to evaluate the treatment of cognitive symptoms associated with dementia and the other was designed and conducted to evaluate the incidence of tardive dyskinesia in elderly patients treated with olanzapine.

Individual clinical study reports for each of the studies have been previously submitted to the appropriate IND or NDA. Reference is made to the following submissions:

- F1D-MC-HGAO (Treatment of Patients with Psychosis Associated with Dementia, acute phase only); submitted on September 21, 1995 to NDA 20-592
- F1D-MC-HGAO (Treatment of Patients with Psychosis Associated with Dementia, extension phase only); submitted on May 1, 2003 to IND 28,705 Serial No. 898
- F1D-MC-HGEU (Treatment of Psychosis and Behavioral Disturbances Associated with Alzheimer's Disease, acute phase only); submitted on October 5, 1998 to NDA 20-592 (S009) and withdrawn on August 27, 1999; re-submitted on May 2, 2003 to IND 51,457 Serial No. 066
- F1D-MC-HGEU (Treatment of Psychosis and Behavioral Disturbances Associated with Alzheimer's Disease, extension phase only); submitted on April 23, 2003 to IND 51,457 Serial No. 065
- F1D-US-HGGV (Management of Behavioral Disturbances and/or Psychosis in Demented Nursing Home Patients); submitted on November 19, 1999 to IND 51,457 Serial No. 037 within IND annual report
- F1D-MC-HGGU (Treatment of Psychosis and Associated Behavioral Disturbances in Patients with Dementia); submitted on August 12, 2002 to IND 51,457 Serial No. 062
- F1D-US-HGGE (Tardive Dyskinesia in Elderly Patients); submitted on December 20, 2002 to IND 28,705 Serial No. 886
- F1D-US-HGIC (Cognitive Symptoms in Subjects with Mild to Moderate Alzheimer's Disease without Psychosis); submitted on April 29, 2003 to IND 58,551 Serial No. 016
- F1D-MC-HGIV (Treatment of Psychosis With or Without Associated Behavioral Disturbances in Patients with Alzheimer's Disease); submitted on July 28, 2003 to IND 51,457 Serial No. 067

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In summary, efficacy results from these studies were not sufficient to support the intended new indications, however, Lilly would like to discuss with the Division the results of our analysis of the safety information from the above studies.

BACKGROUND/REGULATORY HISTORY

Reference is made to our initial submission to NDA 20-592, approved September 30, 1996, which provided the safety results from the acute phase of Protocol F1D-MC-HGAO and also to our efficacy supplement NDA 20-592 S009; submitted October 5, 1998 and withdrawn on August 27, 1999, which provided safety results from the acute phase of Protocol F1D-MC-HGEU. Based on results from these 2 studies and discussions with the Division, our current approved labeling includes a PRECAUTION regarding the safety of olanzapine in Alzheimer's dementia patients. This labeling language was approved with the acute bipolar mania indication in March 2000.

QUESTIONS FOR DIVISION

Question 1

Based on our review of the integrated safety data from seven clinical studies provided in the document entitled "*Safety Review of Olanzapine Clinical Trials Conducted in Elderly Patients with Dementia*", Lilly believes that a labeling change is warranted. We are proposing to include the following new paragraph under WARNINGS:

Safety Experience in Elderly Patients with Dementia-Related Psychosis — In elderly patients with dementia-related psychosis, the efficacy of olanzapine has not been established. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs. 1.5%, respectively). After adjusting for differences in duration of treatment, the exposure-adjusted mortality rate in olanzapine-treated patients was not significantly different from placebo-treated patients. Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age >80 years, sedation, concomitant use of benzodiazepines and presence of pulmonary conditions (e.g., pneumonia, with or without aspiration).

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We are also proposing to update the Dysphagia, Use in Patients with Concomitant Illness and Geriatric Use sub-sections under PRECAUTIONS (changes are shown as strikethrough for deletion and large font for new text):

Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. ~~Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in the placebo-treated patients. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia.~~ Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Use in Patients with Concomitant Illness — ~~In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of the placebo-treated group, where at least 1 placebo-treated patient was reported to have experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be drug related. In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (see WARNINGS).~~

Geriatric Use — Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years of age or over. In patients with

schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with ~~various psychiatric symptoms in association with Alzheimer's disease~~ dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Does the Division agree that the proposed labeling provided above and in Item 2 of this submission is appropriate based on the safety results provided in the "Safety Review of Olanzapine Clinical Trials Conducted in Elderly Patients with Dementia"?

Question 2

Of the studies included in the integrated safety evaluation, two studies included active comparator treatment groups. Study HGGU included a risperidone treatment group (randomized, double-blind study); Study HGGE (randomized, open-label study) included a treatment group of patients receiving various conventional antipsychotics. Crude mortality incidence and exposure-adjusted mortality rate were not significantly different between olanzapine- and risperidone-treated patients [crude incidence: 2.9% vs. 2.0% and exposure-adjusted rate: 12 per 100 patient-years vs. 8 per 100 patient-years, respectively]. In Study HGGE, crude mortality incidence and exposure-adjusted mortality rate were not significantly different between olanzapine- and conventional antipsychotic-treated patients [crude incidence: 14.8% vs. 16.1% and exposure-adjusted rate: 18 per 100 patient-years vs. 22 per 100 patient-years, respectively].

Furthermore, reference is made to FDA Medical Review dated June 12, 2002 for NDA 21-436 (aripiprazole). In this review, the FDA medical reviewer noted that in the completed placebo-controlled trial in Alzheimer's disease patients (study 138006), the acute phase (10 week) mortality rate in the aripiprazole group was 3.8% (4/105) versus 0.0% (0/102) in the placebo group ($p=0.12$). Since exposures in the two groups were comparable, exposure-adjusted rates were not computed. For comparison, in the olanzapine placebo-controlled dementia database, crude mortality rate in the olanzapine group was 3.5% (42/1184) versus 1.5% (7/478) in the placebo group ($p=0.024$). The exposure-adjusted mortality rate was 11 per 100 patient-years for olanzapine versus 5 per 100 patient-years for placebo [95% CI: 0.789-1.481 vs. 0.192-0.983, respectively].

In evaluating the aripiprazole pooled Alzheimer's dementia trials [studies 138004, 138005, 138006], the FDA medical reviewer noted an all-cause crude mortality rate of 7.7% (39/504) in aripiprazole-treated patients compared with 0% (0/102) in placebo-treated patients. The adjusted mortality rate in the pooled trials was 17.4 per 100 patient-

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years. These mortality rates are comparable to a crude mortality rate of 4.8% and adjusted mortality rate of 14.4 per 100 patient-years in olanzapine-treated patients from the olanzapine overall integrated dementia database [studies HGAO, HGEU, HGGE, HGGU, HGGV, HGIC and HGIV].

Based on the safety comparisons of olanzapine with risperidone and conventional antipsychotics in our integrated safety database, along with our understanding of the aripiprazole safety data, an increased risk of mortality in patients with dementia-related psychosis strongly suggest a class effect.

Does the Division believe that this safety result may represent a class effect and should lead to updated antipsychotic labeling across the class?

SUBMISSION INFORMATION

This submission is provided in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs," also referred to as the Electronic Submissions Guidance. In order to add clarification and perspective, the following comments provide information on the content and format for this supplement.

Submission documents are located under Item 1 (Table of Contents), Item 2 (Labeling), Item 8 (Clinical) and Item 20. Item 2 is located under the *Labeling* folder and Item 8 is located under the *Clinstat* folder. Item 20 is located under the *Other* folder. Items 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19 are not applicable to this submission.

Cover Letter

Sponsor request for a meeting is provided in the cover letter.

Item 2 (Labeling)

A copy of the annotated and unannotated proposed labeling text is included in Item 2.

Revised labeling text is proposed in the WARNINGS and PRECAUTIONS section of currently approved labeling. Revised labeling text supported by results from the integrated safety review is annotated by electronic links to the document titled "Safety Review of Olanzapine Clinical Trials Conducted in Elderly Patients with Dementia" included in this submission.

Item 8 (Clinical/Statistical)

A safety review of integrated safety data from seven clinical studies of olanzapine in elderly patients with dementia titled "Safety Review of Olanzapine Clinical Trials Conducted in Elderly Patients with Dementia" is included in Item 8.

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